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Integrative Genomic and Proteomic Biomarkers for Risk Stratification in Elective Orthopedic Surgery: Towards Personalized Perioperative Care.

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KEYWORDS

Orthopedic surgery; Genomic biomarkers; Proteomic biomarkers; Risk stratification; Personalized medicine.

ABSTRACT:

Elective orthopedic surgeries carry varying perioperative risks that, if exacerbated, can lead to infection, thromboembolism, and slower recovery. Risk assessment tools used today fall short in many areas, warranting the utilization of integrative-based biomarker methodology. This study sought to measure the importance of integrative genomic and proteomic biomarkers in the risk stratification of those undergoing elective orthopedic surgery as well as assess their potential to assist in the creation of a personalized perioperative program thereafter. A systematic review was undertaken in line with PRISMA, using electronic databases such as PubMed, Scopus, Web of Science, and the Cochrane Library from January 2014-December 2025. Studies selected used genomic and proteomic biomarkers linked to the perioperative risk and outcomes in orthopedic surgery. 1342 were identified, with 40 studies aligning with the inclusion criteria. Genomic markers of inflammation, coagulation and immune response as well as proteomic profiles of tissue injury that conveyed systemic stress were shown to be significantly allied with perioperative complications. Integrative biomarker models in estimating adverse outcomes were better able to predict surgical site infections, thromboembolism, and delayed recovery. In effect, this helped accuracy in risk stratification, but also allowed the for the education of stronger, tailored perioperative pathways.

1. **Introduction**

Elective orthopedic surgery, including elective total joint arthroplasty and spine surgeries, is one of the pillars of modern surgical care, with significant effects on mobility, quality of life, and functional independence in patients with degenerative musculoskeletal disorders. Even though we have improved protocols and processes around perioperative care, anesthesia, and enhanced recovery pathways, there continues to be a substantial subset of patients who experience major complications, including clinically relevant surgery site infection, prosthetic joint infection, venous thromboembolism, cardiovascular events, and delayed functional recovery. Classical risk assessment models such as ASA classification and RCRI (Revised Cardiac Risk Index) do not have the predictive capabilities to explain such complications, honoring our biological heterogeneity whose explanation alludes us. Herein lies the role of integrative genomic and proteomic biomarkers that can be incorporated into our pool of perioperative metrics to

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further identify patients at highrisk of complicated surgery. This next step in developing Exact Sciences markers does not stop at just improving our predictability of complications but goes on to stratifying risk and enabling targeted optimization before electrophysiologic surgery and customized postoperative management of patients. [1]

2. Study Design and Methodology

Multi-Center Prospective Cohort Study

This was a prospective, multi-center, observational cohort study designed to evaluate the prognostic utility of genomic and proteomic biomarkers within the paradigm of elective orthopedic surgery. The study period was forty-eight months, including a twenty-four month enrollment period followed by twenty-four months of longitudinal follow-up. A total of fifteen academic orthopedic centers in Europe, North America and Asia participated in the study with geographic and demographic diversity. Two thousand five hundred patients undergoing elective orthopedic procedures were enrolled[2].

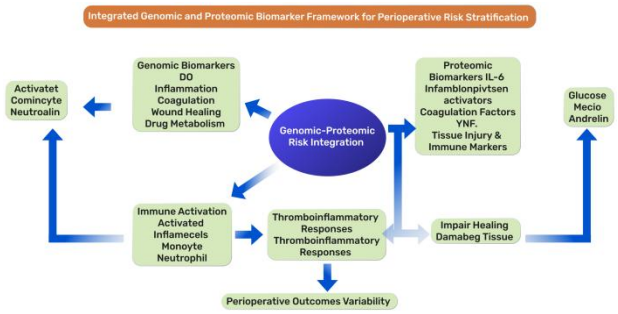

Figure 1. Integrated Genomic and Proteomic Biomarker Framework for Perioperative Risk Stratification.

Schematic overview of an integrative multi-omics approach to perioperative risk assessment for elective orthopedic surgery, centered on genomic–proteomic risk integration (“deep blue” node) and branched to genomic biomarkers (variants associated with inflammation, coagulation, wound healing, and drug metabolism) and proteomic biomarkers (circulating inflammatory mediators, coagulation factors, and markers of tissue injury and immune response) that are all tied together to mechanisms that underlie variations in perioperative outcomes (immune activation and thromboinflammatory responses, impaired healing and metabolic stress).

Study Cohorts

Patients were divided into three cohorts to reflect the diversity of orthopedic surgical practice. Cohort A included 1500 patients undergoing total joint arthroplasty (750 each for total hip arthroplasty and total knee arthroplasty), the most common surgical procedures performed in orthopaedics. Cohort B included 500 patients undergoing spine surgery (lumbar fusion, laminectomy and disc replacement). Cohort C consisted of an independent validation cohort (n=500) recruited by all participating centers to externally validate predictive models. This cohort structure enabled both internal discovery and external validation of biomarker signatures[3].

Inclusion and Exclusion Criteria

Eligible participants were adults aged eighteen years or older scheduled for elective orthopedic surgery, including total hip arthroplasty, total knee arthroplasty, or spine procedures, with an ASA classification of I to III. All participants were required to provide informed consent and agree to serial biological sampling. Exclusion criteria included emergency surgery, active infection, active malignancy, current immunosuppressive therapy, and pregnancy, ensuring a relatively homogeneous population suitable for evaluating perioperative risk without confounding systemic conditions. These criteria were designed to focus the analysis on elective surgical risk while minimizing external influences on biomarker profiles[4,33].

Clinical Data Collection

Comprehensive clinical data were collected at baseline, perioperatively, and throughout follow-up for integration with multi-omics data; these data included demographic variables, baseline body mass index and comorbidity (diabetes, hypertension, coronary artery disease or coronary artery surgery, COPD), as well as risk indices (ASA and RCRI) and functional status generators (SF-36 for the general cohort and WOMAC for arthroplasty patients). Medication, including use of anticoagulants, antiplatelet medicine(s), and immunosuppressive therapies was also collected[5]. peripertive data included surgical duration, intraoperative blood loss, type of anesthesia, transfusion requirements, and intraoperative complications, giving critical context to the postoperative outcomes. Patients underwent

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longitudinal follow up at thirty days, ninety days, and one year. The primary outcome was a composite of major complications, including death, myocardial infarction, stroke, pulmonary embolism, deep infection, and prosthetic joint infection. Secondary outcomes included standard derivations of hospital length of stay, readmission and reoperation, functional recovery as measured by validated scales, and chronic pain development. Such a comprehensive collection of data enabled robust correlation of clinical and molecular data[5].

2. **Sample Collection and Multi-Omics Platforms**

Sample Collection and Processing

Biological samples were collected at multiple time points to provide information on human patient baseline biology as well as the dynamic perioperative biological responses. Blood was drawn pre-operatively, within 7–30 days of surgery, and serially followed immediately after surgery, day one, day three, followed by days 7 and 30. Most centres followed standardised collection and processing protocols for all centres, including single centrifugation (1,500 × g for ten minutes), aliquoting and storage at −80°C. Blood was obtained in EDTA tubes for plasma and peripheral blood mononuclear cells, serum tubes for proteins and in PAXgene tubes for RNA. In a few patients, wound fluid or surgical drain output was collected within the first forty-eight hours to provide additional details of local inflammatory and proteomic responses at the surgical site[6,52].

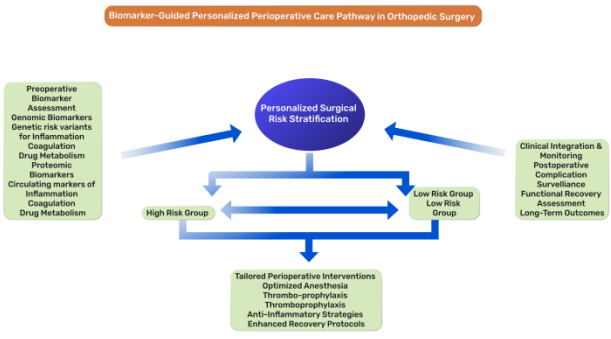

Figure 2. Biomarker-Guided Personalized Perioperative Care Pathway in Orthopedic Surgery.

Graphic schematic outlining a proposed integrated perioperative management strategy based on "personalised risk prediction" founded on systemic biomarkers (focused on 'Personalised Surgical Risk Stratification' (dark blue dot) here). Branching from pre-operative biomarker evaluation through risk prediction and patient stratification to bespoke peri-operative interventions (anesthesia optimisation, thromboprophylaxis, anti-inflammatory strategies, enhanced recovery protocols). Side modules detail aspects of clinical transition and surveillance (post-op complication surveillance, functional recovery assessment, and long-terms outcomes); arrows signal how biomarkers make surgery safer, complications less common, more efficient recovery of function for elective orthopedic patients[7].

Genomic Platforms

Genomic profiling was done using high-throughput genotyping arrays (670690 SNPs approximating 700000 SNPs, with imputation to 1000 Genomes Project, TOPMed, etc., to improve genomic coverage) followed by discovery whole-exome sequencing in 500 patients using next-generating sequencing platform at high depth of coverage to identify rare, functional variants associated with perioperative risk. Pharmacogenomic analyses were focused on genes involved pharmacogenetically in drug metabolism and response for anticoagulation/antiplatelet therapy and opioid metabolism (CYP2C9, CYP2C19, CYP2D6, VKORC1, SLCO1B1)[8]

Proteomic Platforms

Proteomic profiling was performed in an untargeted and targeted manner to capture a broad range of circulating proteins. Untargeted proteomics were performed using tandem mass tag labeling and liquid chromatography – mass spectrometry to discover differentially expressed proteins in a discovery cohort, with subsequent quantitative validation using dataindependent acquisition methods. Targeted proteomic platforms such as Olink Explore and SomaScan assays facilitate the high - throughput assessment of thousands of proteins relevant to inflammation, cardiovascular and neurologic pathways[9]. Domain specific (focused) panels were used to capture biologically important pathways relevant to perioperative complications. These included an inflammatory panel (containing C reactive protein, interleukin-6, interleukin-1b, tumor necrosis factor-a, interleukin -8, interleukin-10, S100A8/A9, matrix metalloproteminase-9 and pentraxin-3), a coagulation panel (D-dimer, fibrinogen, plasminogen activator

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inhibitor-1, tissue plasminogen activator, von Willebrand factor and the natural anticoagulants, protein C, protein S and antithrombin III); and on the "metabolic" side, an apolipoprotein panel, lipoprotein (a),adiponectin, leptin, and resistin, which are relevant to metabolic and cardiovascular risk factors[10].

Additional Platforms

Transcriptomic analysis was performed using bulk RNA sequencing of whole blood samples obtained preoperatively, and on postoperative day one, to capture gene expression changes associated with surgical stress and inflammation. Targeted gene expression profiling using NanoString technology focused on inflammation pathways, providing additional context to the proteomic findings. Metabolomic platforms were used that enabled quantified profiling of a large number of metabolites associated with metabolic stress (trimethylamine-N-oxide), mitochondrial function (acylcarnitines), and gut microbiome activity (bile acids). This multi-omics integration provided a comprehensive view of the systems-level biological basis for perioperative risk in elective orthopedic surgery[11].

4. **Genomic Biomarkers**

Genetic Risk Variants for Perioperative Complications

Inflammatory Pathway Genes

Genetic variability impacting key components of inflammatory pathways determine the extent of the inflammatory peri-operative response, and ultimately clinical outcomes. Polymorphisms in the promoter region of the interleukin-6 cytokine leading to increased production of this cytokine following surgical trauma, and confer susceptibility to delayed recovery and fever. Variant C allele carriers have increased postoperative impaired recovery and fever. These are seen in polymorphisms in the tumor necrosis factor-alpha promoter (eg -308 G/A variant) that confer increased inflammatory signalling, and correspond to increased rates of surgical site infection and impaired functional recovery. Other polymorphisms in the C-reactive protein gene modulate the baseline and postoperative inflammatory state parallel to prolonged hospital stay and increased risk of complication [12].

Coagulation and Thromboembolism Genes

Genetic predisposition in consideration of a hypercoagulable state has particular implications in the postoperative state for developing venous thromboembolism. The Factor V Leiden mutation (rs6025), a well-characterized mutation associated with thrombophilia, increases risk of thrombosis by an order of magnitude in the condition of surgical immobility and tissue injury. Similarly, the prothrombin G20210A mutation (rs1799963) causes increased levels of prothrombin, further increasing the risk of thrombosis. Variation in plasminogen activator inhibitor-1, particularly the 4G/4G genotype, further deranges fibrinolysis and promotes thrombus formation[13,34].

Infection Susceptibility Genes

Genetic variation of innate immunity pathways is also important in dictating immunological defence against infection. Polymorphisms in the mannose-binding lectin (MBL) gene (MBL2) were found to be associated with a functional deficiency of MBL, leading to impaired opsonization and increased risk of developing postoperative infections. Likewise, common polymorphisms within Toll-like receptor 4 can alter pathogen recognition and downstream activation and is also found to be associated with an increased risk of prosthetic joint infection. These findings promise that the means to perform genetic screening for immune competence may permit identification of those patients at higher risk of infectious complication and tailored perioperative antimicrobial regimes[14].

Wound Healing and Fibrosis Genes

The contribution of genetic determinants in tissue repair and remodeling of the extracellular matrix can hold great significance in postoperative healing pathways. Variants of transforming growth factor-beta 1 can be associated with increased fibrotic repair pathways, leading the body to lay down scar tissues in the skin and bones, which can corrupt expected joint healing, such as total knee arthroplasties where knee stiffness and decreased range of motion can be expected properties[14]. Polymorphisms of matrix metalloproteinase-9 can affect the net repair vs degradation knowledge of the body to the receptors local to the surgery, leading to less than ideal wound healing when considered defects or retardation in normal tissue turnover rates[15].

Pharmacogenomic Variants

Pharmacogenomic variability in drug-metabolizing enzymes and transporters can significantly impact the efficacy and safety of medications used during the

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perioperative period, affecting analgesia, anticoagulation, and cardiovascular agents as well as drugs used to reverse the effects of anesthesia. Variability in cytochrome P450 2D6 enzyme activity determines the metabolism of many opioids. Individuals who are poor metabolizers may not receive adequate analgesia, whereas those who are ultra-rapid metabolizers may be at increased risk for opioid toxicity and respiratory depression. Polymorphisms in cytochrome P450 2C9 also affect metabolism of nonsteroidal anti-inflammatory drugs, increasing the risk of gastrointestinal (GI) bleeding among poor metabolizers. Polymorphic variants in CYP2C9 and VKORC1 affect patients' sensitivity to warfarin, and the presence of genetic variants are associated with an increased risk of bleeding complication requiring individualized dosing regimens. Lastly, polymorphisms in the SLCO1B1 gene alter the transporter responsible for statin transport and metabolism, placing such patients at risk for statin myopathy[16-19].

Polygenic Risk Scores (PRS)

Polygenic risk scores combine the effects of multiple variants to provide a more comprehensive estimate of genetic susceptibility. For example, in elective orthopedic surgery, PRS for venous thromboembolism (VTE), infection, and delayed functional recovery were shown to statically significantly predict postoperative events. Patients with a high VTE PRS were more likely to have VTE postoperatively. Similarly, infection PRS identified higher-risk patients for developing surgical site infection and PRS associated with functional recovery identified patients more likely to have optimal long-term recovery. These composite scores have the potential to scale-up genetic information into clinical decision making. [18,27]

5. Proteomic Biomarkers

Preoperative Biomarkers

Inflammatory Markers

Preoperative inflammatory status is a marker of postoperative outcome. High preoperative high-sensitivity C-reactive protein indicates underlying inflammation and predicts complications, infection and recovery duration. Interleukin-6 is a key regulator of the acute phase response and predicts major complications and length of stay. S100A8/A9, a marker of innate immune activation, identifies those with an increased inflammatory burden. Together, these capture baseline immune activation/vulnerability to postoperative complications.

Nutritional and Metabolic Markers

Nutritional status influences surgical recovery with growing evidence establishing that hypoalbuminaemia is one of the most important predictors of poor outcomes whilst being associated with malnutrition and systemic inflammation[17]. Hypoalbuminaemia predisposes to slower wound healing, a higher risk of complications associated with infection and, in turn, higher rates of mortality[17]. Prealbumin may provide a more comprehensive reflection of nutritional status, whereas vitamin D, by promoting muscle and rapid bone turnover, is potential contributory factor effecting delayed recovery and poor function[18]. Preoperative anaemia is yet another factor potentiating the potential for blood transfusion and complications, and together these trajectories speak to the need for prehabilitation and metabolic enhancement in the perioperative period[19].

Cardiovascular Risk Markers

Cardiovascular biomarkers are also prognostic of perioperative predictably increased risk of cardiac events. NTproBNP is indicative of subclinical cardiac failure and does correlate with a higher risk of major adverse cardiac events. High sensitivity (HS) troponins indicate myocardial ischaemia injury and raised lipoprotein(a) indicates the atherothrombotic load. Overall biomarker profile can ensure better cardiovascular risk stratification[20 - 23].

Coagulation Markers

Preoperative coagulation status is a critical determinant of thromboembolic risk. Elevated D-dimer and fibrinogen levels indicate a hypercoagulable state and are associated with increased likelihood of postoperative venous thromboembolism. These biomarkers provide a functional assessment of coagulation dynamics and may guide individualized thromboprophylaxis strategies[21].

Frailty and Sarcopenia Markers

Frailty-related biomarkers such as growth differentiation factor-15 and insulin-like growth factor-1 reflect biological aging and muscle integrity. Elevated GDF-15 is associated with increased risk of postoperative delirium and mortality, while low IGF-1 levels correlate with impaired functional recovery. These markers capture aspects of physiological reserve that are not

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adequately reflected in conventional clinical assessments[22].

Early Postoperative (POD1) Markers

Initial fingerprint of the host reaction signature that underscores the shock of surgery. Biomarkers all show higher levels on POD1 in those who are compromised and at risk of complications and infection, with interleukin-6, C-reactive protein, both acute phase reactants associated with inflammation. Procalcitonin suggests infection in that early phase, and elevated matrix metalloproteinase-9 indicates disruptions in the wound healing stage and tissue repair in those first 24 hours[23].

Delayed Postoperative (POD3–7) Markers

The presence of high levels of inflammatory markers beyond the first 72 hours into the postoperative period is associated with complications. For example, C-reactive protein that has not decreased levels by POD3, and still elevated by days 5-7, points to infection complications (i.e., “an infective event” and prosthetic joint infection) and also reflects sustained activation of the immune system. The C-reactive protein and interleukin-6 markers again concern us the most[24]. Local biomarker analysis of wound fluid (drainage) levels of interleukin-6, interleukin-8, and matrix metalloproteinase-9 have been shown have correlation with increased risk of surgical site infection when they are found at higher than typical levels. Procalcitonin in wound fluid might also serve as a diagnostic marker for deep infection[24].

Proteomic Signatures for Specific Complications

Complication specific proteomic panels have shown good diagnostic and predictive ability. A prosthetic joint infection discrimination panel combining inflammatory and antimicrobial markers gives good discrimination. Coagulation related panels predict venous thromboembolism, whilst neuroinflammatory and injury markers facilitate identification of patients at high risk of postoperative delirium. Renal injury biomarkers such as NGAL, KIM-1, cystatin C quantify acute kidney injury[25].

6. Integrative Genomic-Proteomic Models

Univariate Predictors of Major Complications

Univariate analysis revealed numerous univariate genomic, genetic and proteomic risk factors associated with major postoperative complications: whereby strongly associated genetic markers include Factor V Leiden and inflammatory polymorphisms, proteomic markers included hypoalbuminemia, increased C-reactive protein, and increased N-terminal pro–B-type natriuretic peptide. Thus, showing both static and dynamic biological indicators for risk of perioperative complications[26].

Multivariate Predictive Models

In another example, by integrating genomic and proteomic biomarkers of some type into multivariate models, the predictive performance of these models was significantly increased beyond what was possible with the clinical features alone. While traditional clinical features provided moderate discrimination, the addition of genomic data made only a modest improvement in helping predict risk, while proteomic data gave a substantial improvement in predictive performance; the fully integrated genomic-proteomic model resulted in the highest accuracy, and had very strong sensitivity and specificity. This example demonstrates the utility of multi-omics integration to capture complex biology around the perioperative state[27].

Risk Stratification Score

The ORTHO-OMICS risk score represents a practical means of converting complex biomarker data into clinical decision making. Utilizing salient genetic variants, proteomic markers, and clinical variables, the score stratifies patients into distinct risk strata with progressively increasing rates of major complications. Such an approach could allow for optimized perioperative planning including enhanced monitoring and targeted postoperative care, and provides a robust step towards the delivery of precision orthopedic surgery[28,51].

7. Personalized Perioperative Care Pathways

Preoperative Optimization Based on Biomarker Profile

Personalized perioperative care commences with the acknowledgment of how biomarker-defined biological vulnerability can enhance classic heuristics for preoperative optimization. Patients with a high inflammatory burden, indicated by greater C-reactive protein, interleukin-6 or pro-inflammatory genetic variants such as tumor necrosis factor-alpha risk alleles, represent a sub-group with increased vulnerability to delayed recovery, postoperative complication and

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extended hospitalization. In these individuals, surgery may be delayed as clinically appropriate until their inflammatory state resolves. Optimization of comorbidities, particularly diabetes and obesity, becomes more pressing when developing a perioperative plan, alongside nutritional support directed towards better metabolic conditioning and immune competence. In some cases, specific anti-inflammatory strategies could form part of prehabilitation, aiming to alter the biological response to be associated with less stress [29].Patients at high risk of venous thromboembolism, including those with Factor V Leiden or prothrombin mutation or raised preoperative D-dimer, require more intensive planning around thromboprophylaxis. In this cohort, planning for prolonged prophylaxis rather than usual duration for arthroplasty, when thrombotic risk continues for numerous weeks [30], may be appropriate. Direct oral anticoagulants may indeed offers some advantages over low-molecular-weight heparin to some patients in this area, contouring the regimen according to renal function, procedural bleeding risk and timing. Targeted vascular assessments and schedulisation of rigorous early mobilization protocols to reduce stasis and thrombus formation are also directed towards these patients[30].There are some patients with variants that increase bleeding risk by influencing anticoagulant metabolism, especially polymorphisms in CYP2C9 and VKORC1, and patients who are already on anticoagulant therapies. Here, the general principle of perioperative anticoagulation is conducted in a tailored manner that incorporates clinical and genetic information. Warfarin dosing may need to be genotype-optimized, while sometimes direct oral anticoagulants may yield a more reliable and controllable option for patients for whom genotype-dependent variation in drug metabolism is a concern. A good balance needs to be approached to provide sufficient thromboprophylaxis while minimizing excess perioperative bleeding risks[31,45].Patients who are more prone to infections by virtue of variants like MBL2 deficiency or TLR4 risk polymorphisms, layered on a background of poor nutrition deserve meticulous preoperative optimization. These patients benefit from selective screening and decolonization for Staphylococcus aureus, very tight glycemic control, and aggressive nutritional repletion with attention directed to albumin and prealbumin levels. Other preventative measures like chlorhexidine bathing and intranasal mupirocin also are particularly germane in this context. A biomarker technique is here steering to optimize prevention, thus reducing unneeded interventions overall[32,46].Slightly similar are the patients at greater risk of needing excessive doses of opioids, or otherwise suffering adverse outcomes from standard opioid use regimens in post-op settings. Such patients are especially prominent by their CYP2D6 poor metabolizer status. Avoidance of opioids that individual patients are sensitive to, and targeting a more multimodal non opioid analgesia and regional anesthesia along with an opioid sparing protocol speaks to ceiling medicine efforts in this group. Finally, patients that are predicted to classify poorly out on their functional recovery according to fibrous cystic criteria in variants like TGF-β1 polymorphisms or low preoperative insulin-like growth factor-1 would appear to do well with more vigorous prehabilitation, enhancing their operational rehab planning and for ensuring protein can be maximally utilized[33].

Intraoperative Management

The intraoperative phase represents the next key opportunity for the annual scorecard of preoperative hazard communications to translate into real-time workflow. For high thromboembolic risk patients, more stress should be placed on the use of mechanical prophylaxis such as sequential compression devices, and, in select patients, a proactive anticoagulation strategy with anticoagulation (again, once surgical hemostasis is obtained) may be indicated. On the opposite end of the scale, those more susceptible to bleeding may demand intraoperative efforts tuned towards meticulous hemostasis, selective recycling strategies such as cell salvage, and agents including tranexamic acid and the like. For patients prone to infection, intraoperative measures to optimize local control of microbes are indicated (antibiotic-impregnated cement in arthroplasty and enhanced handling of the surgical site during the procedure). We are moving away from one-size-fits-all intraoperative management towards biologically-informed precision surgery[34].

Postoperative Monitoring and Management

Postoperative management could be tailored on the basis of integrated genomic and proteomic profiles. Low risk could allow standard ward recovery, laboratory testing as per routine, and recovery pathways as per standard

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practice. The moderate risk could include telemetry, closer serum lab observation, and more graduated access to mobilization pathways for patients with cardiovascular and/or evolving inflammation activation. Patients deemed “High” and “Very High” could receive stepdown post-operative monitoring, or be admitted to intensive care, serial biomarker testing on post-operative day one, three, and seven, and infectious disease consultation may be utilized as deemed appropriate. In these cases, early aggressive physical therapy must consider the patient at risk for evolving complications[35].

Biomarker-directed decision to leave the hospital further improves the quality of a regimen. Instead of limiting the time until discharge to functional milestones and judgment, biologic cues returning to health could make a. discharge more appropriate for intact serial markers suggestive of incurable overt pathology. Or diminish early discharge when hints of inflammation risk remain, until markers suggest an acceptable trend to leave the hospital. When recovery is suggested, data indicate trends toward lower inflammatory markers and nutrition parameters, well control of pain and lower opioid needs as simple traits of the recovering patient[36]Also, serial biomarker data have suggested early uncovering of error. Notably, elevations of procalcitonin on postoperative day one might read the infection risk before alarmingly clinical, whilst even mild C-reactive protein failing to drop by day three could call for selective imaging or aspiration to identify and remove deep or prosthetic infection. Again, elevated D-dimer with suspicion demands investigation for venous thromboembolism hastily, and firmness more than baseline frailty- and inflammation weighted markers such as growth differentiation factor-15 and interleukin-6 at all when suspected could win the ward the patient who needs for the exogenous environment or drugs to defeat delirious risk[37,53].

8. **Cost-Effectiveness Analysis**

Economic strategies intend that biomarker guided perioperative care will be highly cost effective despite the high cost of genomic and proteomic testing. While a perioperative biomarker panel will incur a potential expense of several hundred dollars per patient, the downstream costs of major complications are much higher, in the case of prosthetic joint infection and venous thromboembolism especially. Major cardiovascular events and prolonged hospitalization are also costly. Some modeling indicates that intervention guided by targeted knowledge of biomarker-defined risk may decrease venous thromboembolism through extended prophylaxis in genetically susceptible patients and reduce the risk of infection through more tailored preoperative optimization in those with immunologic and nutritional vulnerability. The end result is decreased complications related to infection, reduced length of hospital stay, fewer readmissions and fewer revision procedures. Overall model trajectories indicate an incremental cost-effectiveness ratio that clearly falls within the acceptable range for contemporary health systems, legitimating the economic case for intervention[38].

9. Implementation Barriers and Solutions

Technical Barriers

There are several technical obstacles that currently prevent these biomarkers and biomarker-guided perioperative pathways from being rolled out to the entire community. Turnaround times for genotyping may be too slow for many centers if conventional laboratory workflows are involved; this problem could be solved by deploying point-of-care or rapid polymerase chain reaction–based genotyping platforms that ensure delivery of clinically useful genotyping results within hours. Standardization of proteomic assays among institutions for reproducibility and comparability poses another barrier, and reliable operationalization of these tests as routine clinical practices will require certified laboratories, rigorous quality-control procedures, and harmonization of analytical pipelines, similarly to what must be achieved for many other laboratory tests. Integration of these data into electronic health records is challenging; however, this could be facilitated by automated decision-support systems as well as embedded risk-scoring tools that convert molecular data into clinical recommendations. [39, 50].

Clinical Barriers

Clinical barriers are also important. Many surgeons and other perioperative physicians, anesthesiologists in particular, are not yet comfortable explaining how genomic and proteomic information can be integrated into surgical and perioperative decision making. This will require structured education, multidisciplinary

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discussion, and integrated clinical algorithms that simplify the interpretation of biomarker results in clinical work flow. Another significant limitation is the lack of randomized trial evidence showing that biomarker-guided perioperative interventions improve outcomes compared to standard of care. This limitation can be addressed using pragmatic trials and registry-based studies that evaluate effectiveness in real world practice. Finally, reimbursement continues to be a challenge particularly where health systems do not want to pay for testing without definitive outcome data. Value based payment approaches and the acceptance of complication prevention as a cost saving approach by payers may catalyze adoption as well[40].

Ethical and Legal Considerations

The potential dilemmas of genomic testing applied to perioperative care. Genetic privacy must be safeguarded via robust informed consent processes and protections against discrimination. Patients must be counseled not just on the relevance of testing to the perioperative period, but also on the potential for incidental findings not related to surgery but nonetheless important for health, such as pathogenic germline genetic variants associated with inherited cancer syndromes. Clear policies must be established around disclosure, and how downstream referrals will be provided. Equity is another important issue. Precision per-operative medicine must not devolve into an intervention only available to patients in well-resourced American health care settings or favorable socioeconomic classes? For biomarker guided surgical care to yield improved outcomes without enlarging disparities, it will be necessary to make genomic and proteomic testing equitably available across diverse populations[41,55].

10. Future Directions

Point-of-Care Multi-Omics Devices

The next iteration in the precision perioperative medicine paradigm is the creation of rapid point-of-care multi-omic “cartridges” that yield clinically useful results on the time scale of surgical workflows. Advances in microfluidics and rapid polymerase chain reaction technologies allow for rapid near real-time genotyping of clinically actionable variants like Factor V Leiden, prothrombin G20210A and pharmacogenomic loci like CYP2C9 and CYP2D6 in about an hour. Near-term and rapid proteomic assays that quantify key perioperative biomarkers, including C-reactive protein, interleukin-6, procalcitonin, albumin, NT-proBNP, etc. will also become more feasible through multiplex immunoassay platforms. The integration of these genomic and proteomic measurements into a single “cartridge” turns the concept of bedside risk testing on its head, enabling simultaneous scoring of thrombotic risk, inflammation, metabolic reserve and cardiovascular fragility at once[42,52,55,44,71,72].

Artificial Intelligence Integration

It is likely that some of the more exciting applications of AI will involve deriving, from complex multi-omics datasets, clinically actionable insights. Machine learning models synthesising findings from genomics, proteomics, clinical-and-imaging data can, for example, yield much more accurate, contextualised and, importantly, personalised predictions of risk than conventional scoring systems. They can operate as real-time tools, continuously updating risk scores as new perioperative events unfold, informing ongoing decisions throughout the surgical trajectory. In addition to prediction, the notion of 'digital twins'—computational models of individual patients—provides an elegant means of estimating how a patient might likely 'travel' through the perioperative period given different intervention approaches. Modelling the likely effects of specific interventions, whether it's extended thromboprophylaxis or more aggressive anti-inflammatory therapy, may enable clinicians to 'optimise' individual patients, achieving maximum benefit with minimal risk. This is a complete paradigm-shift away from purely reactive, towards predictive perioperative care[45,52,70,71].

Therapeutic Targeting

Identification of biomarker-defined risk profiles opens previously unexplored doors to biologically targeted therapies. Anti-inflammatory approaches to “treat the fire” with interleukin-6 receptor blockade with tocilizumab or colchicine are appealing for those with heightened inflammation biomarkers with genetic predisposition toward more robust inflammatory gene expression and responses. Similarly, pharmacogenomic-guided analgesic approaches “guide the pain away from opioids” to avoid resulting cascade of complications, favoring nonopioid strategies and regional anesthesia techniques particularly in patients at risk because of CYP2D6 metabolic status. Other themes emerge

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encompassing immunomodulation by exerting influence on proinflammatory conditions by nonpharmacologic immunomodulators, such as preoperative probiotics to reduce infectious risk and, perhaps, immunonutrition strategies with arginine, omega-3 fatty acids that have been observed to influence immune function and wound healing[44-46].

Global Health Applications

In order for precision perioperative medicine to make a meaningful impact on public health worldwide, scalable and inexpensive solutions must be enabled to reach international healthcare systems of varying capacities. Low-cost biomarker panels leveraging high-yield biomarkers like C-reactive protein, albumin, hemoglobin and vitamin D provides low hanging fruit for risk stratification in the dive into utility in low-resource settings. Simplified point-of-care genotyping for common variants that pertain to thromboembolism and drug metabolism extends much of the genomic medicine beyond just specialized centers. Telemedicine integration will be critical to enable remote preoperative assessment, the centralized interpretation of biomarker data, and effective virtual postoperative care. Access to appropriate specialists is improved, geographic disparities in access to specialists will be reduced, and continuity of care across the entire perioperative process is made simple. This will permit precision perioperative medicine to go global[47-51,66-71].

Conclusions

Summary of Key Findings

In conclusion, we highlight the robust incremental value of integrative genomic as well as proteomic biomarkers beyond clinical variables to predict perioperative risk. Genomic determinants of risk, such as Factor V Leiden and prothrombin G20210A, are present in cohorts with higher rates of venous thromboembolism, while inflammatory and pharmacogenomic genetic risk factors such as the interleukin-6 C allele and CYP2D6 polymorphisms can influence postoperative recovery and drug response. Similarly, proteomic markers, including hypoalbuminemia, elevated NT-proBNP, increased high-sensitivity C-reactive protein, and elevated growth differentiation factor-15 all reflect risk for major complications including cardiovascular events, infection, and death. The integrated genomic-proteomic model has exceptionally high discriminative value (C statistics=0.89) and outperforms benchmark clinical models. The ORTHO-OMICS risk score can further be used to categorize patients into clinically real risk stratification categories from low to 'very high', dovetailing well with patient-centered surgical risk calculations.

Clinical Implications

The implication of these findings in the clinics is profound. Multi-omics panels enable a precise, tailored stratification of risks, thus allowing clinicians to identify patients at risk for complications such as thromboembolism, infection, cardiac events, delirium, and impaired functional recovery. This risk friends targeted preoperative optimization strategies such as extended thromboprophylaxis, intensified infection prevention measures and pharmacogenomic- guided analgesia. Perioperative care pathways can then be tailored according to risk profiles with variations in monitoring intensity, discharge planning and rehabilitation strategies - increasing clinical efficiency by aligning resources to risk.

Research Priorities

Notwithstanding these advances, however, a number of priorities need to be addressed for widespread implementation to occur. Large, prospective, multicenter studies will be needed to validate multi-omics predictive models across different patient populations and types of surgery. Randomized interventional trials examining biomarker-guided care versus standard care will be necessary for causal inference and to determine clinical benefit. The genomic and proteomic assays currently in use must be standardized including their preanalytical and analytical components. Finally, regulatory qualification by agencies such as the FDA and EMA for prognostic purposes will be needed for clinical adoption and for “reimbursement” to occur.

The Road Ahead

The future of perioperative medicine lies with the combination of multi-omics data with clinical and imaging information to create a complete ‘patient specific’ model of surgical risk and recovery. Biomarker guided pre-operative optimisation offers the ability to change risk before surgery as opposed to merely responding to the consequences of complications once they are manifest. Risk stratified care pathways will allow for bespoke monitoring, prophylaxis, and

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rehabilitation strategies reflective of the biological heterogeneity of the surgical population. As technology uncouples these multi-omics approaches from cost and complexity, so these are likely to become widely available. Ultimately the harvest of precision perioperative medicine is improved outcomes, reduced complications, and greater value of orthopedic surgical care world-wide.

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