Review Article

Patient-tailored prevention of post-operative complications after lung resection

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Abstract: Precision medicine, according to the Precision Medicine Initiative, is an emerging medical approach for disease treatment and prevention that takes into account individual variability in genes, environment and lifestyle for each person. This approach is rapidly evolving especially in the field of medical oncology where it has significantly transform cancer care. The ultimate aim of tailoring therapeutic strategies is to maximize the benefit an individual patient harnesses from the specific treatment, while at the same time decreasing the impact of adverse side effects associated with it. Medical oncology is currently leading the way with the ability to identify the specific genetic mutation and allocate the treatment that is most likely benefitting the patients. In thoracic surgery, there is still a gap between our evidence-based guidelines that offer recommendations for groups of patients and the ideal individual approach recommended by the precision medicine. This paper aims to identify areas where it is possible to apply precision medicine to the prevention of postoperative complications after thoracic surgery.

Keywords: Precision medicine; thoracic surgery; postoperative complications; prevention

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Precision medicine

Precision medicine has three main goals:

- Offering therapeutic decisions tailored to single patients;
- Offering targeted therapies;
- Offering customised strategies.

To achieve these goals, precision medicine uses diagnostic tests and analysis of clinical data to select the most appropriate treatment for the individual.

The critical question that the recently published enhanced recovery guidelines try to answer is "what is the optimal preoperative management for patients undergoing lung surgery?"

The key question for precision medicine is "what is the optimal preoperative management for Mr. Smith that is currently undergoing lung surgery?" (1).

This paper aims to explore if it is possible to fill the gap between these two questions and to move from recommendations that are good for a group of patients to recommendations that are good for the single patient in the area of prevention of postoperative complications after lung resection.

Evolution of thoracic surgery

The modern thoracic surgical practice has come a long way from its inception. Various innovations and development in anaesthesia, microbiology and improved understanding of respiratory physiology and homeostatic balance in response to surgical stress have provided the impetus to the advancement of thoracic surgery. We have progressed

from post-operative mortality of over 40% to the current reported mortality of about 2% in lobectomy undertaken as treatment for lung cancer (2). The climate under which thoracic surgeons practice has also undergone a rapid transformation in the recent decade. It has transitioned from an autocratic practice to one of shared decision-making, in partnership with the patients (nice.org.uk). As we continue the renaissance of thoracic surgery, ongoing effort is put into improving all aspects of care to ensure standardised care and excellent outcomes.

Clinical guidelines: a step towards precision

Clinical guidelines, a mean to standardise care, have become ubiquitous in clinical practice, and thoracic surgery is no exception. The Institute of Medicine defined clinical guidelines as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'. It is a tool frequently used by clinicians to ensure more consistent and efficient care and to implement the practice of evidence-based medicine to achieve optimal outcomes for patients.

One example of a guideline recently published that has had a considerable impact on thoracic surgery is the Guidelines for enhanced recovery after lung surgery: recommendations of the enhanced recovery after surgery (ERAS) and the European Society of Thoracic Surgeons (ESTS) (EJCTS 2018) (1). It is based on the principles of enhanced recovery using systematic multimodal perioperative care pathway and patient involvement to improve outcomes and patient experience after thoracic surgery. This guideline considered various pre-, peri- and post-operative interventions to optimise patients as much as possible.

Current guidelines are useful in ensuring standardisation of care, optimisation of patient and optimal outcomes. One of the limits of the guidelines is that the evidence that informs them is gathered from groups of patients, we should be cautious and aware of potential pitfalls and recognize that occasionally, an individualized approach with deviation away from guidelines may be necessary or specific patient-tailored intervention in addition to routine care may be necessary to optimize outcomes further. As stated in the ERAS guidelines, in some instances, good quality evidence may be lacking, or evidence may be misleading or misinterpreted. It is also not practical to think that every aspect of thoracic surgical practice can be tested in appropriate and well-designed clinical studies (3).

Precision medicine in other clinical areas

There are many examples of such precision medicine in clinical practice, where a more targeted and specific patient-tailored approach to the individual has to be taken across a range of medical and surgical specialities such as point-of-care testing of platelet inhibition to guide antiplatelet therapy in patients with cardiovascular disease and targeted immunotherapy in oncology patients with the presence of specific mutation (4,5).

Risk scores to assess where you are on the continuum

There is a continuum that goes from surgery that is appropriate for a group of patients to surgery that is chosen and designed for the individual patient.

The first step in identifying where the patient stands in this continuum is a risk scoring system. A search in the literature will show that there are countless studies on risk scores. Risk scores have many uses, namely allowing better-informed consent and shared decision-making process, identifying high-risk patients needing further functional assessment and optimisation, as an aid in resource utilisation peri-operatively, aid in surgical strategy and perhaps targeted post-operative care (6). An ideal risk score should give an accurate estimate of the risk of mortality and morbidity of the proposed procedure. Many of the current risk scores in thoracic surgery are developed to estimate only the risk of perioperative mortality, not morbidity. There are many risk scores, but none has been widely accepted as the ideal scoring system or gold standard (7-9). In the current climate, there are ongoing efforts and research dedicated to finding the holy grail of risk score in thoracic surgery. In the absence of the ideal risk score in thoracic surgery, the practice may differ widely between units in risk assessment of thoracic patients. In our unit, we adhere to the guidelines in preoperative assessment by the British Thoracic Society where a combination of Thoracoscore, post-operative predicted lung function tests, cardiovascular risk assessment using the revised cardiac risk index (RCRI) and anaesthetic assessment to determine if further functional assessments such as cardiovascular exercise testing may be indicated. These patients are subsequently discussed at our weekly complex case review with our anaesthetic and nursing colleagues to plan surgical strategy such as limited resection and further targeted post-operative care such as admission

to critical care post-operatively. There is some evidence to suggest these forums play a role in ensuring high-risk patients are not unnecessarily declined radical treatment but at the same time ensuring good outcomes (10).

One of the many reasons why the ideal and gold standard mortality risk score in thoracic surgery continues to evade us is due to the low mortality observed in thoracic surgery in the modern era. However, post-operative complications (PPC) generally are much more common, in the region of 15% (11). In thoracic surgery, recent papers describing the development of a new risk score reported cardiopulmonary morbidities between 9–18% (7,12). Is there a role in identifying patients at high risk of various complications specific to thoracic surgery and how can we improve outcomes by applying a more targeted and precise approach to the post-operative management of these patients?

No matter what the targeted approach is, we believe that the general principles of enhanced recovery should still apply and form the fundamentals of post-operative care bundles. We are also keen to explore how the principles of enhanced recovery could be tailored as much as possible towards the individuals rather than towards groups of patients.

Application of precision medicine to common post-operative thoracic surgical complications

We will next consider the various common post-operative thoracic surgical complications (pain, air leak, pulmonary related postoperative complications and cardiovascular complications) and consider whether there is evidence that allows a targeted or patient-tailored specific approach to prevent, pre-empt and manage these.

Pain control

Pain is one of the most common consequences of surgical procedures. A multimodality approach to pain control focuses on preoperative, intraoperative and postoperative factors. Even though that one of the main pillars of enhanced recovery is to reduce the use of opioids, these drugs are still used to ensure the patient is comfortable enough to mobilise, to comply with physiotherapy and to be able to expectorate and breathe effectively.

In this area, we find one of the possible applications of precision medicine.

It is well-known that opioids cause sickness and nausea. It is also well-known that a group of patients will not metabolise the drug precursor to active component and therefore will not experience the benefit of the administered drug. On the other hand, another group of patients will metabolise the drug exceptionally quickly and therefore will experience the benefit of the drug for a shorter period (13). This difference in the way patients metabolise opioids is linked to the cytochrome P450-2D6. The cytochrome metabolises codeine to morphine that is the active metabolite with pain relief action. There are four phenotypic subgroups of cytochrome P450-2D6. The respective number of functional alleles defines the subgroups. We recognise ultra-rapid, extensive, intermediate and poor metabolisers.

Patients with ultra-rapid phenotype are at higher risk of severe toxicity due to a higher level of morphine released from the codeine in a short period. Patients with the poor metabolizer phenotype experience ineffective pain relief due to the reduced formation of morphine.

It is possible to then to identify how a patient will metabolise opioids with a simple genetic test. If this test was used routinely, in a Caucasian population about 7% to 10% of patients will avoid experiencing side-effects or ineffective pain control from the use of opioids like codeine, tramadol and oxycodone (14) (https://www.sciencedirect.com/topics/medicine-and-dentistry/cyp2d6).

Also, the same testing would be able to prevent side effect due to pharmacological interaction with drugs that use the same metabolic pathway (15).

Prolonged air leak (PAL)

PAL is probably one of the most prevalent and undesirable complications following elective thoracic surgery. The definition of "prolonged" varies from 5 days (Society of Thoracic Surgeons General Thoracic Surgery Database, North America) to 7 days (National Minimum Dataset for Thoracic Surgery and Lung Cancer Surgery by the Society for Cardiothoracic Surgery in Great Britain). Regardless of the exact threshold, the unanimous consensus is that persistent air leak is significant if it causes delayed discharge from the hospital.

The incidence reported in the literature varies between 6–18%. PAL is undesirable because it prolongs hospital stay and recovery, adds to patient discomfort, increases the risk of other complications such as empyema and ultimately increases cost. Since 2010, there have been multiple efforts in the first instance to establish models to predict patients

at higher risk of developing PAL (16-20). So far, these studies are mainly retrospectively using various definitions of PAL and different cohort of patients (some focused solely on VATS lobectomy patients, some included all-comers including patients undergoing lung volume reduction surgery and bullectomy). These studies identify risk factors (FEV1 <80%, male sex, BMI <18.5, MRC dyspnea score >1, TLCO <80%, smoker and pleural adhesions) that can be used to recognise patients at higher risk of developing PAL. At this point, we have some measures that can be put in place to optimise the journey of this group of patients.

In general, the guidelines for enhanced recovery after thoracic surgery recommend that these patients should be screened for nutritional state preoperatively and oral nutritional supplement instituted for malnourished patients, preoperative smoking cessation and regarding chest drain management, the use of digital drain and avoidance of suction.

There are some surgical strategies suggested in the literature to minimise PAL. Among those there are limited fissure dissection or no fissure dissection, accurate selection of the stapler used for fissure completion, the use of buttressed staplers, a meticulous assessment for aerostasis at the end of the procedure, the use of sealants, minimal lung re-inflation at the end of surgery and potentially limiting pleural space by performing pleural tent. There are not many evidence available to support these strategies. There was a report from a single institute describing a standardised approach used by a single surgeon to reduce PAL by using a fissureless anterior approach technique to lung resection, use of buttress staplers and protocol-driven chest drain management post-operatively (21). Using this approach, they found less PALs in patients undergoing both lobectomies and sublobar resections with reduced hospital stay compared to a cohort of patients in the Society of Thoracic Surgeons National Database. However, it did not describe the precise selection criteria for inclusion of patients to this approach except that patients who underwent bilobectomy and redo surgery were excluded. Evidence for buttress staplers is only available in animal models (22) (https://www.medtronic.com/covidien/en-gb/products/surgical-stapling/endo-gia-reinforced-reload.html). A Cochrane review published in 2010 on surgical sealant for preventing air leaks after pulmonary resections in patients with lung cancers found 16 randomized controlled trials comparing a variety of sealants (biological and synthetic) (23). 6 trials showed a significant reduction in PAL, 3 trials showed a significant reduction in time to drain removal, and 3 trials showed a significant reduction in length of hospital stay. Although some trials showed a significant reduction in PAL and time to drain removal, these were not necessarily associated with the reduction in length of hospital stay. Hence, the review does not recommend the use of sealants with the aim of reducing the length of hospital stay.

The lack of evidence for some of the surgical strategies does not necessarily imply that it is ineffective in preventing PAL in the high-risk patients, as the intervention was applied to all patients regardless of their risk for developing PAL. In our unit, we use a variety of targeted perioperative approach in these patients as described above such as careful selection of staplers (including the use of buttress staplers), slow firing of staplers especially in fissure completion, fissureless dissection in lobectomy, meticulous assessment of aerostasis at the end of the procedure with aggressive intervention to achieve aerostasis such as suturing, further staplers or use of sealants, gentle re-inflation at the end of the procedure and avoidance of suction in the management of chest drain if possible.

Regarding postoperative air leak, it is possible to customise the pre-operative, intraoperative and postoperative management to a group of patients who are at higher risk of developing this complication. The tailoring of the preventive and corrective measures is still at the level of the group rather than at the level of the single patient.

Pulmonary-related PPC

Another possible target for precision medicine is the complications that are included in the group of pulmonary-related PPC. The incidence reported in the literature ranged from 2% to 40%. It is a combination of atelectasis, sputum retention and pneumonia. Pulmonary infection is the main reason for delayed discharge in patients undergoing elective thoracic surgical procedures (24). Other than an economic cost, PPC has been found to affect both short and long term outcomes. Post-operative mortality was significantly higher in cohorts of patients after lung resection for lung cancer that developed PPC, as high as 30% reported in one study (25,26). PPC does not only have a negative impact on immediate survival, but it is also associated with poorer long-term cancer survival after lung resection (27,28).

Despite a common and significant co-morbidity, very little is known about the exact incidence and cause of this dreaded complication. First of all, the exact definition of pneumonia post-operatively may be challenging to diagnose as radiological changes and increased inflammatory

response are both common after thoracic surgery. There are various tools to aid the diagnosis such as the Melbourne Group Score (MGS) diagnostic criteria that required 4 out of 8 clinical and radiological features to be present in 24 hours. MGS was found to perform better than other tools in the diagnosis of PPC in thoracotomy patients (29). Patients with underlying lung disease such as pulmonary fibrosis, interstitial lung disease and severe emphysema are intuitively thought to be patients of the higher risk of developing PPC. Other factors identified as possible risk factors described in the literature include older age, smoking, COPD, low BMI, impaired FEV1, perioperative bronchial colonization with potentially pathogenic microorganism, post-operative higher pain score, and type or extent of resection (25-27,30,31).

To offer personalised prevention and management, we need to identify modifiable risk factors. As in any clinical situation, there are inherent risk factors that are not modifiable such as age, the presence of parenchymal lung disease and the extent of resection required. Regarding the other factors instead, the general principles of enhanced recovery cover a broad aspect of practice that aims to mitigate the risks of developing PPC such as attention to nutritional state preoperatively, smoking cessation, optimal pain control and aggressive physiotherapy and mobilisation post-operatively.

There is no gold standard risk stratification to identify objectively the high-risk cohort of patients undergoing thoracic surgery who will develop PPC post-operatively. Based on the guidelines issued by the British Thoracic Society in the radical management of patients with lung cancer, patients with post-op predicted FEV1 or TLCO <40% are considered high risk of developing postoperative complications and mortality and further cardiovascular assessment such cardiopulmonary exercise testing (CPET) is recommended to stratify these risks further. VO2 max/kg/min between 10–15 is considered moderate risk, and thorough assessment and counselling is recommended. VO2 max/kg/min <10 is considered high-risk, and surgery may not be the optimal treatment option. Assessment of ventilatory efficiency found that VE/VCO2 of >35 is associated with high-risk of developing PPC.

Once the high-risk patient is identified a multidisciplinary discussion is usually helpful to fine-tune the extent of resection (wedge *vs.* segment *vs.* lobectomy), to explore the possibility of lung-sparing procedures (sleeve resection) and to clarify the risk and benefit of the recommended surgery versus alternative treatments. In our unit, this discussion happens in a multidisciplinary meeting that we call "Complex care review meeting" and is attended by surgeons, thoracic anaesthetists, intensive care doctors, lung cancer nurse specialist.

The finalised outcome included recommendations about operability, operative strategies such as the extent of lung resection, pre- and perioperative optimisation and post-operative care.

Prehabilitation

In selected patients with poor respiratory capacity, early-stage cancer and motivated patients, we usually recommend prehabilitation with the aim to improve respiratory reserve and decrease PPC. The Official American Thoracic Society/ European Respiratory Society Statement defined pulmonary rehabilitation as a comprehensive intervention based on a thorough assessment followed by patient-tailored therapies, that include but are not limited to exercise training, education and behaviour change designed to improve the physical and psychological condition of people with chronic respiratory disease (32). Pulmonary rehabilitation has been shown to be effective in patients with COPD such that completion of rehabilitation is mandatory in consideration for surgical intervention.

However, the evidence in lung cancer resection patients is lacking. Pulmonary rehabilitation in chronic lung diseases such as COPD and pulmonary fibrosis has shown improvement in exercise capacity. Patients with poorer exercise capacity are thought to be at high risk of PPC. Intuitively, if we improve the exercise capacity of these patients before surgery, this may decrease the risks of PPC post resection. A recent review could not establish the optimal exercise intervention programme for patients undergoing treatment for NSCLC either pre- or post-operatively due to the lack of substantial evidence (33,34). There are various studies, albeit small, that demonstrated the improvement in exercise capacity in patients with lung cancer and impaired respiratory function, but not directly correlated to postoperative outcomes. Prehabilitation in a study resulted in significantly better VO2 max/kg/min 60 days postoperatively, but this study did not assess the length of hospital stay or PPC (35) directly. In a couple of small observational studies, pulmonary prehabilitation before lung resection leads to significantly lower incidence of PAL, PPC and shorter LOS (36,37). A small RCT randomising patients undergoing lung resection to pre-habilitation or usual care found no difference in overall

postoperative complications or LOS, although PPC was significantly lower in the pre-habilitation group. Unfortunately, evidence regarding the benefits of pre-habilitation in high-risk patients undergoing lung resection lacks due to non-randomisation of study and non-selectiveness of the patient cohort, i.e. the RCT included all patients undergoing lung resection rather than focus on high-risk patients such as those with impaired lung function, active smoking or increased bronchial responsiveness.

In summary, we have scoring systems that can identify a group of patients at higher risk of complications. There are also measures available with different degree of evidence that can minimise the risk and reduce the overall burden of complications. For some patients the preoperative optimisation starts with pre-habilitation, for all the others the enhanced recovery guidelines offer the current best practice to prevent pulmonary complications. Also, there is some evidence supporting the use of mini-tracheostomy to aid clearance of secretions and prevent sputum retention, and regular mucolytics and nebulisers.

In a similar way to what we have seen in the management of air leak, the tailoring of the preventive and corrective measures is still at the level of the group rather than at the level of the single patient.

Cardiovascular (CVS) complications

Another possible target for precision medicine is in the prevention and management of cardiovascular complications. The occurrence of one of these complications negatively impacts surgical outcomes, increase length of hospital stay and increase the cost of care. CVS complications include arrhythmias, myocardial infarction (MI) and pulmonary oedema. Sometimes, studies report a composite of cardiovascular and pulmonary complications together, but according to the literature, cardiovascular complications after major lung resection occur in 10–15% of patients (38).

There are several small studies to assess the effects of lung resection on the right and left ventricular function. In patients with normal right ventricular function preoperatively, pneumonectomy but not lobectomy, significantly reduced the pulmonary vascular bed, which leads to progressive pulmonary hypertension, although not necessarily causing right ventricular dysfunction (39). Both lobectomy and pneumonectomy were found to adversely affect the diastolic function of the left ventricle at 2–4 weeks post lung resection (40).

BTS guidelines recommend the use of the RCRI to assess the risk of cardiovascular complications. The first step in identifying patients who may require more patient-tailored interventions is to identify active cardiac conditions. In those without active cardiac conditions, RCRI of 3 or more warrants further evaluation and optimisation guided by the results of the evaluation. The risk factors listed in RCRI are high-risk surgery (which includes all thoracic surgery), history of ischaemic heart disease, history of congestive cardiac failure, history of cerebrovascular disease, insulin therapy for diabetes and serum creatinine of more than 177 μmol/L.

As for many conditions in medicine, there is a degree of controversy regarding the importance of cardiac comorbidity. Some studies found that cardiac co-morbidity such as ischaemic heart disease had no impact on CVS complication after lung resection (41-43). The small number of thoracic procedures (only 12%) included in the development of RCRI might be responsible for its poor performance at predicting CVS risk in lung resection patients (44). Subsequently, a revised RCRI, the thoracic revised cardiac risk index (ThRCRI) was developed specifically to improve the risk stratification of CVS risk in patients undergoing thoracic surgery (44). ThRCRI seemed to have a better discriminatory index and was validated using single institution's database as well as the extensive database maintained by the Society of Thoracic Surgeons General Thoracic Database (12,45,46).

Atrial fibrillation (AF) is probably the commonest CVS complication subtype in lung resection and extensively studied. The incidence of postoperative AF (POAF) may be as high as 40% (47). POAF may be caused by direct cardiac injury, endogenous and exogenous cardiac stimulations, inflammation and right heart burden (48-50). POAF is extensively studied and reported in various retrospective series, with multiple risk factors identified such as male sex, increasing age, lung cancer, general anaesthesia, open surgery, extent of resection, increasing operating time, history of ischaemic heart disease, conversion from VATS to open and post-operative infection (51-53). Most of these factors are not modifiable. Recently a retrospective study specifically assessed factors associated with POAF that are modifiable such as excess alcohol intake, red cell transfusion, use of inotropes but not vasopressor and open surgery (54).

Perioperative MI, on the other hand, is not a typical occurrence post lung resection. The diagnosis of perioperative MI may be rather difficult. ST-elevation is extremely rare whereas non-ST-elevation MI is 40 times more frequent (55). Besides, after lung resection, ECG

changes such as higher heart rate, increased incidence of atrial arrhythmia, ST changes, P-vector and QRS-vector are common (56). Troponin assay is a useful cardiac marker of choice as thoracic surgery is not usually associated with elevated troponin. A retrospective study found that patients with elevated troponin assay are at high risk of early mortality (57). In these patients, most did not have classical pain or symptoms suggestive of acute coronary event, but rather troponin assay was requested due to POAF, hypotension or dyspnea. Possible risk factors are poor cardiac capacity, diabetes mellitus, chronic renal insufficiencies, cerebrovascular disease, hypertension, smoking, dyslipidaemia, anaemia, significant intraoperative blood loss, blood transfusion, perioperative hypotension, recent percutaneous intervention with stents and suboptimal analgesia (58). Major adverse cardiac events and mortality were significantly higher in patients undergoing lung resection within 1 year of coronary artery stenting (59).

Our review of the literature shows how it is possible to identify patients at higher risk of cardiovascular complications. The medical history, the physical examination and the cardiac risk index help to mitigate the risks of CVS complications mainly because they help to re-direct patients with active cardiac conditions towards cardiac intervention.

The treatment of the underlying cardiac disease and the pharmacological optimisation of the patient offers at the moment the best option to avoid postoperative complications. Patients who are identified at higher risk are investigated more with second line tests like echocardiography, CPET, coronary angiography and stress MRI. Once the investigations are completed, these patients are often discussed with our cardiology colleagues to determine risks and optimisation of their cardiac conditions that include medical, percutaneous and even surgery if indicated. Patients with a history of excessive alcohol intake are also optimised by referral to Alcohol Liaison Team and usually admitted a few days before surgery to manage and avoid acute withdrawal.

For CVS complications, in the group of patient with active cardiac comorbidity, it is possible to minimise the risks offering treatment for the cardiac condition in advance of thoracic surgery.

Operative factors

We have considered mainly preoperative patient factors and the ongoing effort to define risk factors, and by identifying these risk factors, attempt to ameliorate its impact on the outcomes.

There is limited data on specific operative factors that directly influence the postoperative outcomes, especially in the immediate post-operative period. Extent of resection, i.e., sublobar compared to lobar or extended resection is known to affect both early and late outcomes. However, there is very little the surgeon can do to alter this as it is dictated by the extent of the cancer and patient-related factors.

With the advent of minimally invasive video-assisted thoracoscopy surgery (VATS), there were multiple reports that showed that open thoracotomy significantly predict post-operative morbidity with patients undergoing thoracotomy more likely to develop both pulmonary and cardiovascular complications (60,61). Longer duration of anaesthesia and longer operating time also seem to adversely affect outcomes (62,63). In patients with operating time longer than 180 minutes, the incidence of air leak was higher and length of hospital stay longer (64). The same authors also develop a risk score consisting of 4 factors, namely male gender, presence of hilar or interlobar lymph nodes, presence of thick pleura and bullous or centrilobular emphysema, to predict the likelihood of a complex operation. The ability to anticipate difficult and complex operation may allow the team to plan specifically for the patient with specific precise interventions such as ensuring senior or experienced surgeon performing the resection and low threshold for conversion to thoracotomy if VATS approach was adopted. By adopting these measures, this may reduce the operating and anaesthetic time.

Conclusions

It is difficult to personalise the prevention and management of postoperative complications in the same way that oncologists are currently able to target treatment for some cancers with identifiable genetic mutations. The complications that affect thoracic patients fall into broad areas: pain, air leak, pulmonary complications and cardiovascular complications. For air leak, pulmonary complications and cardio-vascular complications the prevention is possible following the recommendations of the enhanced recovery guidelines and as discussed before these recommendations apply primarily to a large group of individuals and only by inference to the individual patient.

The only area where we found the possibility of preventing complications in a targeted way is in the pain management and specifically preventing/minimising the side effect caused by opioids. In this area a simple genetic

test, if broadly used, could give medical professionals the ability to identify patients more prone to side effects/toxicities and patients unable to metabolise the opioid to the active compound and to choose more appropriate medications.

We envision the possibility that in the next years the thoracic surgical community will be able to close the gap between the question "what is the optimal preoperative management for patients undergoing lung surgery?" and the question "what is the optimal preoperative management for Mr. Smith that is currently undergoing lung surgery?".

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