CONFERENCE PROCEEDING

Genomics relevant to the neuroanaesthesiologist

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INTRODUCTION

'It is more important to know what sort of person has a disease, than to know what sort of disease a person has'. ~ Hippocrates (circa. 460–370 BC)

The essence of Hippocrates' observation is coming to fruition 25 centuries later[1] in the understanding of genomics to explain inter-individual variability, and in response, application of the knowledge to improve clinical outcomes. Anaesthesia speciality has been the forerunner for many discoveries and applications in genomics from the infant stages of the field, for example, interactions of barbiturate in patients with porphyria (1937),[2] cholinesterase deficiency leading to succinylcholine-induced prolonged apnoea (1957)[3] and malignant hyperthermia (1962).[4] In the field of neurosurgery, reports of personalised therapy decisions based on genetic, epigenetic and molecular biomarkers have recently emerged – use of candidate molecular markers to complement diagnoses, aid prognosis and allow individualised treatment to patients with glioblastoma multiforme, thereby avoiding unnecessary therapy, reducing toxicity and associated costs.[5] While the decision to operate or not is being aided by genetics, the perioperative period is itself a model of stress and inflammation superimposed on complex disease and is associated with pain and haemodynamic/metabolic shifts[6] – all these elements have a genetic basis for individual response variability. As can be imagined, surgical trauma triggers an integrated neuroendocrine reaction, and the body mounts a counter-regulatory response. The balance between these pro-inflammatory pathways and the response is an individually determined process and affects patient outcomes. This makes it imperative that personalisation be the backbone of patient management during this period.

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Moreover, the patient is exposed to multiple drugs in a short course of time perioperatively. We know that drug response variability is a major factor leading to perioperative adverse reactions, and genetic factors contribute to an estimated 50% of drug response variability.[7] This is because about 59% of drugs cited in adverse drug reactions are metabolised by at least one enzyme with a variant allele known to cause poor metabolism.[8,9] Hence, genomics should play an important role in the practice of anaesthesia today. This is of futuristic importance given projections that by 2020, the number of surgeries will increase by 25%, associated costs by 50% and likelihood of atherosclerotic-related cardiac, cerebral and renal complications by 100%.[6,10,11] Personalised medicine may be the key to preventing these predictions from becoming true.

BASICS OF GENOMICS

The term genetics conjures memories of pea plants and single gene disorders. Genomics refers to all of the genes in the human genome and their interactions with each other, the environment and other cultural and psychosocial factors. The Human Genome Project successfully completed the unravelling of the approximately 3 billion deoxyribonucleic acids (DNAs) base pairs that make up the human genome in April 2003. Before that, we thought there would be about 100,000 genes because there were so many different proteins known. Now, we know that there are about 21,000 genes, many of which can make multiple proteins each. DNA transcription to ribonucleic acid (RNA) and translation to protein indicates that changes in DNA sequences may cause functional or structural changes in proteins. The most common type of allelic variation is single-nucleotide polymorphisms (SNPs) when two alternative bases occur at an appreciable frequency in a population (>1%).[12] Other genetic variations

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are called mutations (incidence <1%) which may be duplications, deletions, insertions, translocation or inversion of DNA segments. However, since more than one codon (triplet of nucleotides) code for the same amino acid, not all mutations cause structural changes in the protein. Another exciting field is of epigenetics, which encompasses non-structural DNA modifications which control gene expression by altering transcription (messenger RNA, microRNA, etc.) via histone modification and changes of DNA methylation.[13] Environmental influences are evident from reports of a high frequency of epigenetic differences between aging monozygotic twins.[14] Besides, proteomics, metabolomics and transcriptomics are evolving areas that are beyond the scope of this report.

PHARMACOGENOMICS RELEVANT TO ANAESTHESIA

It is important to remember that use of an active drug that is metabolised slowly or a prodrug that is metabolised to its active component excessively or by a person with increased receptor sensitivity may cause toxic effects, while an active drug which is metabolised extensively or by a person with reduced receptor sensitivity, may have a reduced effect. This is because of genetic effects on the pharmacokinetics (PKs) and pharmacodynamics of drugs [Figure 1].

Genomics affecting pharmacokinetics of anaesthetic drugs

The major groups of hepatic enzymes involved in drug metabolism are the Phase 1 (cytochrome P450 enzymes, cholinesterases) and the Phase 2 enzymes (uridine glucuronosyl transferases [UGTs] and N-acetyl transferases). Drugs metabolised by different enzyme groups are given in Table 1. While numerous genetic effects on anaesthetic exposure have been described,[9,15] some important clinical implications for anaesthesia are described below:

CYP enzymes

The major CYP450 enzymes of importance to anaesthesia providers are CYP3A4, CYP2D6, CYP2C9 and CYP2C19. Variants of *CYP2C9* (*2, *3) have been associated with decreased enzyme activity and increased risk of bleeding from non-steroidal anti-inflammatory drugs,[16] warfarin[17] and ibuprofen.[18] The drug label for celecoxib carries a Food and Drug Administration warning regarding careful use in *CYP2C9* poor metabolisers.[19] Combination of *CYP3A4*1B* and *CYP3A5*3* variants was found to be associated with decreased fentanyl metabolism in fentanyl-related deaths.[20] The presence of an SNP (G681A) of the *CYP2C19* gene was found to be associated with impaired metabolism of diazepam in a gene-dosage effect manner (4-fold longer half-life in homozygotes and 2-fold longer half-life in heterozygotes carrying the SNP).[21,22] *CYP2B6*6* variant has been associated with increased risk

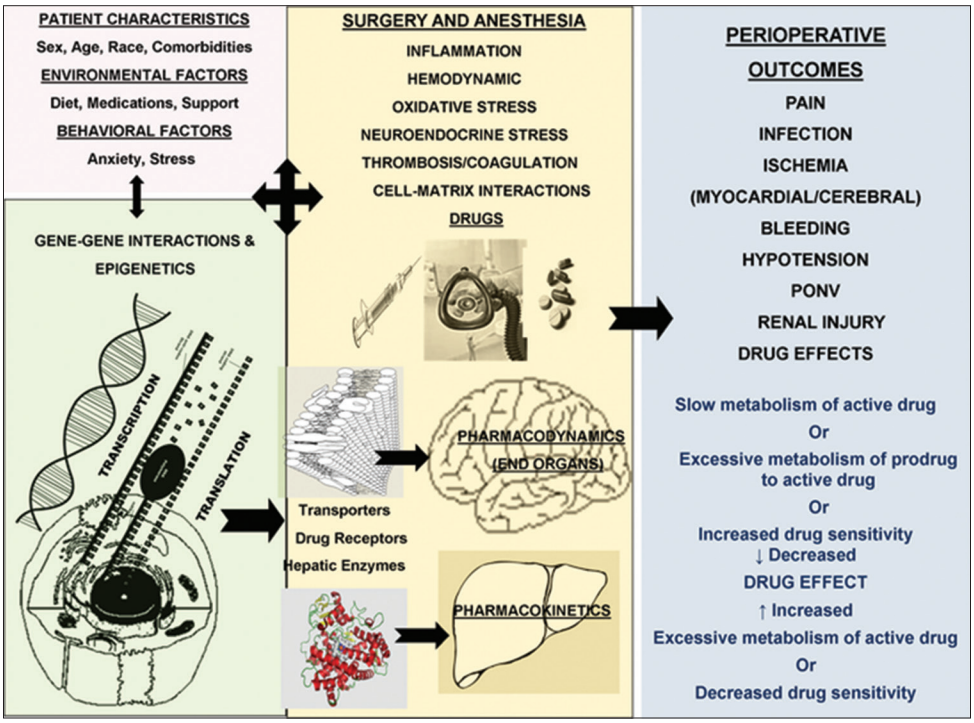

Figure 1: Schematic representation of the effects of an individual's genomics on perioperative outcomes. Gene-gene interactions and environmental influences the person's response to surgical insults and anaesthesia, thereby determining perioperative outcomes. Pharmacogenomic effect on drug responses is also illustrated in simple terms. PONV: Postoperative Nausea and Vomiting

of death from methadone due to decreased metabolism and QTc prolongation.[23,24] *CYP2E1* variant *5 (−1293G>C, −1053C>T) causes increased activity of the enzyme and consequent tendency for halothane hepatitis from exposure to halothane[15] however, may not be an important predictor.

CYP2D6 deserves special mention. Of the federally approved pharmacogenomic information/warnings in the labels of over 100 drugs in the United States, are included analgesics such as codeine and tramadol, which are both metabolised by *CYP2D6*.[19] Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2D6* and codeine therapy are available for clinical practice.[25] O-demethylation of codeine into morphine by *CYP2D6* represents a minor pathway in extensive metabolisers, accounting for 5–10% of codeine clearance in such individuals but is essential for its opioid activity. PK studies show increased conversion of codeine to morphine in *CYP2D6* ultrarapid metaboliser (UM) versus extensive metabolisers[26] which can result in toxic, systemic concentrations of morphine[27] even at low codeine doses. The opioids tramadol[28,29] and hydrocodone[30] show similar effects while the data regarding oxycodone are presently conflicting.[31] Aside from genetics, racial differences contribute to morphine clearance variability with higher clearance observed in African Americans.[32] Furthermore, metabolised by *CY2D6* are the most commonly used agents for post-operative nausea and vomiting (PONV), the serotonin receptor antagonists (ondansetron, palonosetron and dolasetron) and hence are less effective in UM phenotypes andin UMs. Only granisetron is metabolised by *CYP3A4* mainly and may have superior efficacy in *CYP2D6* UM patients.[33]

Table 1: Important genes and variants affecting anaesthetic/analgesic drug pharmacokinetics

Genes	Perioperative medications whose pharmacokinetics are affected by the genetic variants
CYP2B6	Ketamine, propofol, methadone, buprenorphine, meperidine and tramadol
CYP2C8	Diazepam
CYP2C9	Ibuprofen, diclofenac, naproxen, indomethacin, warfarin and phenytoin
CYP2C19	Diazepam, midazolam, barbiturates, tricyclic antidepressants, serotonin reuptake inhibitors and monoamine oxidase inhibitors
CYP2D6	Codeine, tramadol, hydrocodone, dextromethorphan, oxycodone, ondansetron, dolasetron, palonosetron, tropisetron and amitryptiline
CYP2E1	Halothane, sevoflurane, desflurane, isoflurane, acetaminophen and caffeine
CYP3A4	Halothane, ketamine, propofol, midazolam, morphine, meperidine, fentanyl, sufentanil, remifentanil, alfentanil, methadone, amide group (local anaesthetics) and granisetron
CYP3A5	Fentanyl, sufentanil, remifentanil and alfentanil
UGT1A1	Lorazepam, morphine and acetaminophen
UGT1A9	Propofol
UGT2B7	Morphine, ibuprofen, diclofenac, naproxen and indomethacin
BChE	Ester group of local anaesthetics, succinylcholine and mivacurium
5,10 MTHFR	Nitrous oxide

CYP=Cytochrome P450, UGT=Uridine glucuronosyl transferase, BChE=Butyrylcholinesterase, MTHFR=Methylenetetrahydrofolate reductase

Hepatic drug transporters

Hepatic transporters of morphine (organic cationic transporter 1 [*OCT1*]) and morphine metabolites (ATP Binding Cassette C3 [*ABCC3*]) also play a role in morphine PKs. In children undergoing tonsillectomy, the authors found that morphine clearance in homozygotes of loss-of-function *OCT1* variants (*2−*5/*2−*5) was significantly lower (20%) than in wild-type (*1/*1) and heterozygotes (*1/*2−*5).[34] In the same population, they also found that children with *ABCC3* −211C>T polymorphism C/C genotype had significantly higher levels of morphine-6-glucuronide and morphine-3-glucuronide formation (~40%) than C/T + T/T genotypes.[35] These genotypes were also associated with clinical effects such as morphine-induced respiratory depression (personal communications).

Other pharmacokinetic related genes

Another historical example is that of decreased pseudocholinesterase activity associated with >30 genetic variants leading to prolonged apnoea after use of succinylcholine - the two most common variants are the A variant (209A>G, Asp70Gly) and the K variant (1615G>A, Ala539Thr).[36,37] A transversion of 766G>A in the *UGT1A9* gene resulting in the substitution of amino acid D256N was found to increase the risk of suffering adverse effects of propofol.[38] Selzer *et al*. reported the unexpected neurological deterioration of an infant boy after exposure to nitrous oxide twice in a short time.[39] Post-mortem analysis showed 5,10-methylenetetrahydrofolate reductase deficiency in this infant's fibroblasts and a complex combination of mutations in his 5,10-methylenetetrahydrofolate reductase gene including C677T and A1298C SNPs associated with a reduction in the enzyme activity.[40]

GENOMICS AND EFFECTS ON ANAESTHETIC PHARMACODYNAMICS

Anaesthetic effects

Variations in the gene *GABRE*, coding for class epsilon of the gamma-aminobutyric acid type A (GABAA)

receptor (gene map locus Xq28), may explain some of the differential sensitivity to diazepam, barbiturates and propofol [Table 2].[41,42] Volatile anaesthetics act through a different site on the GABAA receptor – a Korean study found a trend for children with the AA genotype in the *GABA*γ*2* nucleotide position 3145 in intron A/G to have increased incidence of emergence agitation, compared to the non-AA group, after sevoflurane anaesthesia in pre-school-aged children.[43] Human melanocortin-1 receptor (*MC1R*) gene is expressed on the surface of melanocytes and affects melanin biosynthetic pathway and pigment formation. Variants of this gene are linked to red hair in women; Liem *et al*. found that red hair is a distinct phenotype linked to increased desflurane anaesthetic requirements that can be traced to three particular mutations of the *MC1R* gene (R151C, R160W and D294H).[44]

B-adrenergic receptor *ADRB2* and vasopressor requirement

Blood pressure variability after neuraxial anaesthesia was found to be predicted by variant Arg16Arg (less hypotension)[45] and Glu27 (more hypotension)[46] in two different studies. A detailed review of the *ADR*β*2* gene can be found in the overview by Litonjua *et al*.[47] and its effects in chronic pain have been studied by Diatchenko *et al*.[48]

Risk of perioperative myocardial infarction

The heritability of myocardial infarction (MI) is striking and well supported by family studies.[49] Common genetic variants on chromosome 9p21 and inflammatory gene polymorphisms[10] (interleukin 6 [*IL-6* − 572G>C]) and two adhesion molecules, intercellular adhesion molecule-1 (*ICAM1* Lys469Glu) and E-selectin (*SELE* 98G>T), were found to be associated with perioperative myocardial injury and mortality after coronary artery bypass.[50-52] Genetic risk factors have also been described for post-operative arrhythmias (*IL-6* 174G/C).[53] Readers are referred to an excellent review on perioperative genomics by Schwinn and Podgoreanu[54] for further elaboration.

Risk of perioperative cerebral ischaemia and cognitive dysfunction

Apolipoprotein E (*APOE*) is the gene responsible for the production of APOE and has been widely studied in relation to cerebral ischaemia, traumatic brain injury (TBI) and Alzheimer's disease. In humans, there are three common isoforms of APOE, encoded by the alleles ε2, ε3 and ε4. Clinical and experimental studies suggest that APOE ε4 is associated with an unfavourable functional outcome after TBI.[55-57] The inheritance of APOE ε4 allele has been mentioned as a risk factor for Alzheimer's disease after TBI although this has not yet been conclusively shown.[58] These effects might be due to differential cerebral blood flow responses in this genotype. Kofke *et al*.[59] found that subjects with Apoε4 genotype showed relative activation of the hippocampus and amygdala in response to increasing doses of remifentanil– they suggest that this differential activation may be important in perioperative cerebral ischaemia involved in cognitive dysfunction and a role for endogenous opiates in Alzheimer's. Several recent trials have highlighted how genetic milieu either increases the pre-disposition for neurologic injury or impairs the ability to recover once that injury has occurred.[60,61] In a large sample (n = 2104), Grocott *et al*. studied association of 26 SNPs and their interactions for association with post-cardiac surgery stroke. Interaction of inflammatory markers C-reactive protein (CRP) and IL-6 SNPs was associated with a significantly increased risk of stroke,[62] with an incidence of 3.09% compared with an incidence

Table 2: Anaesthesia relevant genes affecting perioperative outcomes

Perioperative outcome	Genes implicated
Anaesthetic requirement	Gamma butyric acid receptor gene *GABRE, GABA*γ*2; MC1R*
Vasopressor requirement	*ADR*β*2*
Perioperative myocardial injury/dysfunction	*IL-6, IL-10, ICAM-1, SELE,* factor V; *GNB3; GP1BA*
Post-operative arrhythmias	*IL-6, TNF-a, RANTES*
Perioperative cerebral effects	*APOE, CRP, IL-6,* platelet glycoprotein IIIA *PIA2*
PONV	*DRD2,* M3 muscarinic acetylcholine receptor (*CHRM3*), *FAAH*
Perioperative bleeding	*GPIaIIa, GPIb alpha, tissue factor, prothrombin, tissue factor pathway inhibitor, ACE, PAI-1*
Renal injury	Angiotensinogen, *IL-6, APOE,* angiotensin receptor 1, *eNOS*
Sepsis	*IL-1,* beta *IL-1B, TNF,* CD3d molecule, delta (CD3-TCR complex) *CD3D, PRF1*
Graft rejection	*TNFa, IL-10, IL-1B, ICAM-1, IL-1RN*
Pain	*COMT*
Opioid action/interaction	*ABCB1 OPRM1* gene *FAAH*

MC1R=Melanocortin-1 receptor, ADRβ2=Beta-2 adrenergic receptor, IL=Interleukin, ICAM-1=Intercellular adhesion molecule-1, SELE=E-selectin, GNB3=G-protein-3 subunit, GP1BA=Glycoprotein Ib alpha, TNF-α=Tumour necrosis factor alpha, RANTES=Regulated upon activation normally T-expressed and secreted, APOE=Apolipoprotein E, CRP=C-reactive protein, DRD2=Dopamine receptor D2, CHRM3=Cholinergic receptor, muscarinic 3, FAAH=Fatty acid amide hydroxylase, ACE=Angiotensin converting enzyme, PAI-1=Plasminogen activator inhibitor-1, eNOS=Endothelial nitric oxide synthase, PRF1=Perforin 1 (pore forming protein), IL-1RN=Interleukin-1 receptor antagonist, TCR=T-cell receptor, COMT: Cathechol-o-methyltransferase, ABCB1=ATP-binding cassette B1, OPRM1=μ1 opioid receptor, FAAH=Fatty acid amide hydroxylase, PONV=Post-operative nausea and vomiting, GABRE=Gamma-aminobutyric acid A receptors

of 0.95% in a population without the risk genotypes. This study highlighted a potential mechanistic pathway for perioperative stroke, inflammatory superseded thrombosis-related genes and was similar to that found in risk of MI after cardiac surgery.[62] Genetic makeup and gene expression have been described to contribute to a person's vulnerability to stroke. Numerous genes were implicated; they were induced 1.6–6.8-fold in stroke patients and correctly classified 11/15 patients at 2.4 h, 14/15 patients at 5 h and 15/15 patients at 24 h after stroke.[63,64]

Neuroprotective genes

Mathew *et al*. outlined association of P-selectin (*SELP*) 1087G/A, CRP1059G/C and platelet glycoprotein IIIA *PIA2* polymorphisms with a reduction in overall cognitive deficits after surgery supporting the biologic plausibility of reduced inflammation and platelet activation leading to protective outcomes.[65,66] Besides, certain neuroprotective genes such as erythropoietin, tumour growth factor and hypoxia inducible factor-1 are induced by pre-ischemic stress. This raises exciting prospects for use of viral vectors to potentially deliver neuroprotective genes at high levels to prevent cell death.[67]

Post-operative nausea and vomiting

In a recent genome-wide association study on motion sickness in 80,494 individuals from the 23andMe database, the authors concluded that 35 SNPs involved in balance, glucose homeostasis and other nervous system roles played an important part in motion sickness and likely, PONV too.[68] Besides, correlations have been reported between A2A2 alleles at Dopamine D2 receptor (Taq1A SNP)[69,70] as well as rs2165870 SNP in the promoter region of the M3 muscarinic acetylcholine receptor (*CHRM3*) gene with PONV.[71]

Perioperative bleeding

Post-operative bleeding after cardiac surgery was found to be associated with SNPs of coagulation proteins and platelet glycoproteins (*GPIaIIa* − 52C>T and 807C>T, *GPIb* alpha 524C>T, tissue factor − 603A>G, prothrombin 20210G>A, tissue factor pathway inhibitor-399C>T and angiotensin converting enzyme deletion/insertion).[72] As a corollary, a study evaluating efficacy of tranexamic acid (TXA) in reducing bleeding after cardiac surgery in different genotypes found that 5G/5G homozygotes of the *PAI-1* gene who did not receive TXA had significantly greater post-operative bleeding after cardiac surgery than patients with other genotypes. They also had greater blood-sparing benefit from TXA than the 4G/4G homozygotes.[73]

Other perioperative complications

Studies have shown associations between specific genetic variants and specific post-operative complications;[74] including renal compromise,[75] protection against sepsis (Apoε3),[76] sepsis,[77] inflammatory response and graft rejection after heart and lung transplants.[78]

GENOMICS OF PAIN AND OPIOIDS

Pain perception

Catechol-o-methyltransferase (COMT) is the main enzyme responsible for inactivation of catecholamines including dopamine, epinephrine and norepinephrine. Genotypes of the *COMT* SNPs rs6269, rs4633, rs4818 and rs4680 were grouped into functional haplotypes associated with low-, average- and high-pain sensitivity in adults with non-surgical pain.[79-81] The SNP rs4680 is a common polymorphism of the *COMT* gene on chromosome 22q11 coded by 472G>A, which causes the substitution of valine by methionine at amino acid position 158 (Val158Met). This results in a decrease in *COMT* enzyme activity which leads to high pain sensitivity. In a study of 149 children undergoing tonsillectomy, minor allele carriers of *COMT* SNPs were approximately 3-times more likely to require analgesic interventions than homozygotes of major alleles (*P* value range: 0.0031–0.0127; odds ratio range: 2.6–3.1).[82]

Opioid transport across the blood–brain barrier

The concentration of morphine in brain is influenced by a P-glycoprotein transporter, *ABCB1* at the blood–brain barrier. A polymorphism of *ABCB1*, c. 3435C>T, has been linked with morphine's blood–brain barrier transport activity in adults and the homozygous TT genotype was associated with higher maximum cerebrospinal fluid concentrations of morphine than other genotypes.[83] Previously, *ABCB1* polymorphisms, c. 3435C>T and 1236TT were associated with respiratory depression in Korean adults receiving fentanyl[84] and Turkish adults receiving spinal anaesthesia and intravenous fentanyl.[85] The homozygous diplotype (GG-CC at c. 2677G>T/A and c. 3435C>T) was shown to have borderline association with morphine-induced PONV.[86] Children with GG and GA genotypes of *ABCB1* polymorphism *rs9282564* had higher risks of respiratory depression resulting in prolonged hospital stays after tonsillectomy.[87]

Opioid receptor

Opioid receptor μ1 gene (OPRM1) that codes for this receptor has a functionally significant and common variant called A118G (rs1799971). This SNP causes substitution of an adenine (A) with a guanine (G) at base 118, which in turn causes the amino acid exchange at position 40 of the μ-opioid receptor protein from asparagine to aspartic acid (N40D), leading to the loss of a N-glycosylation site in the extracellular region of

the receptor.[88] Various studies show that individuals with GG genotype require more opioids 24 h following surgery.[89-92] In adolescents undergoing spine fusion, the authors found that the risk of respiratory depression from morphine in patients with AA genotype was significantly higher (odds ratio 5.6, 95% confidence interval: 1.4–37.2, $P = 0.030$).[93] However, the debate is far from over as a meta-analysis by Walter and Lötsch shows.[94]

Opioid-cannabinoid system interactions

Fatty acid amide hydroxylase (FAAH), opioid and cannabinoid systems reciprocally and synergistically modulate functions at multiple levels. *FAAH* codes for an enzyme that hydrolyses anandamide, the 'bliss' molecule. Hence, *FAAH* inhibition increases the bioavailability of anandamide and thereby enhances analgesia; this offers a potential therapeutic target for treating pain and has shown promising potential.[95,96] Five specific *FAAH* SNPs including a missense variant (rs324420) were found to also be associated with more than 2-fold increased risk for refractory PONV in children undergoing tonsillectomy,[97] which shows potentiation of other opioid effects.

CONCLUSION AND FUTURE PERSPECTIVES

The promise and potential for genomics in perioperative medicine is evident from the rapidly increasing plethora of studies showing association of genetic variants with perioperative outcomes and pain. Although many studies deal with cardiac surgery and pain, the results are extendable to neuroanaesthesia. From a translational perspective, these findings are expected to allow prospective risk assessment incorporating genomic profiling of markers important in inflammatory, bleeding, thrombotic, vascular and neurologic responses to perioperative stress; Implications range from individualised a priori pre-operative testing and physiological optimisation, to perioperative decision-making, options of monitoring approaches and critical care resource utilisation. Examples of translational potential are the genomic prescribing system proposed by Ratain to guide therapy,[98] the genotype-based dosing of opioids based on *OPRM1*, *COMT* and *MC1R* proposed by Lötsch and Geisslinger[99,100] and genetic risk signatures for opioid-induced respiratory depression reported by Biesiada *et al*.[101] At present, commercial gene-based assays are available to allow providers to make individualised decisions in prescribing drugs such as psychotropics and analgesics. The Electronic Medical Records and Genomics Network, which was announced in September 2007, is a National Institutes of Health organised and funded consortium of US medical research comprising nine institutions with unique and valuable pioneer experience using a variety of commercial and home-grown electronic health record (EHR). The challenges and solutions for integrating genomic data into the EHR, creation of integrated genomic decision support and the human and electronic processes including standards required for such successful integration are still a work in progress.[102,103]

Technological advances in sequencing and plunging costs are not formidable barriers anymore for clinical implementation[104] in developed countries, although limited by availability of testing facilities. Key factors that still stand in the path of clinical implementation are the difficulties encountered in reliable interpretation of the complex genome-wide data, difficulty in defining reliable phenotypes and questionable generalisation of the findings found in extreme phenotypes, to the general population. The other hindrance remains the lack of awareness and education among providers regarding the advances made in this field and their impact on anaesthetic management. Various human disease variant databases such as the Human Gene Mutation Database,[105] the hand-curated databases ClinVar and MutaDatabase,[106] as well as pharmacogenomics databases (www.pharmgkb.org) are available at the click of a mouse nowadays. Interpretation of genetic findings related to variants not previously associated with human pathology or for which there is limited biological insight (for example, model organisms and biochemical studies) is less straightforward and may rely on in silico prediction algorithms (such as PolyPhen, VAAST and ESEfinder)[107,108] which can easily be fallible.[109] Some other resources are the Encyclopaedia of DNA Elements (www.encodeproject.org) data, that is, an online database of functional elements and the Genotype-Tissue Expression project which aims to provide to the scientific community a resource with which to study human gene expression and regulation and its relationship to genetic variation (www.gtexportal.org).

A strong need remains for prospective, well-powered genetic studies in highly phenotyped surgical populations, which mandate the development of multi-institutional collaborations and multidimensional perioperative databases and establishing perioperative research consortia and standardised protocols for specimen collection, processing, phenotype definition and interpretation. Legal and ethical concerns need to be addressed as well as cost-effectiveness evaluated. Despite all the work that still lies ahead, it is unthinkable at this stage that perioperative approaches remain a random generalised test and try approach, instead of being an individualised patient-specific exercise. Herein lays the realisation of Hippocrates' vision of individualised medicine.

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Conflicts of interest
There are no conflicts of interest.

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