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Genetic mutations associated with susceptibility to perioperative complications in a longitudinal biorepository with integrated genomic and electronic health records

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Abstract

Background: Existing genetic information can be leveraged to identify patients with susceptibilities to conditions that might impact their perioperative care, but clinicians generally have limited exposure and are not trained to contextualise this information. We identified patients with genetic susceptibilities to anaesthetic complications using a perioperative biorepository and characterised the concordance with existing diagnoses.

Methods: Adult patients undergoing surgery within Michigan Medicine from 2012 to 2017 were consented for genotyping. Genotypes were integrated with the electronic health record (EHR). We retrospectively characterised frequencies of variants associated with butyrylcholinesterase deficiency, factor V Leiden, and malignant hyperthermia, three pharmacogenetic factors with perioperative implications. We calculated the percentage homozygous and heterozygous for each that had been diagnosed previously and searched for EHR findings consistent with a predisposition.

Results: Analysis of genetic data revealed that 25 out of 40 769 (0.1%) patients were homozygous and 1918 (4.7%) were heterozygous for mutations associated with butyrylcholinesterase deficiency. Of the homozygous individuals, 14 (56%) carried a pre-existing diagnosis. For factor V Leiden, 29 (0.1%) were homozygous and 2153 (5.3%) heterozygous. Of the homozygous individuals, three (10%) were diagnosed by EHR-derived phenotype and six (21%) by clinician review. Malignant hyperthermia was assessed in a subset of patients. We detected two patients with associated mutations. Neither carried clinical diagnoses.

Conclusions: We identified patients with genetic susceptibility to perioperative complications using an open source script designed for clinician use. We validated this application in a retrospective analysis for three conditions with well-characterised inheritance, and showed that not all genetic susceptibilities were documented in the EHR.

Keywords: butyrylcholinesterase deficiency; factor V Leiden; genotype; malignant hyperthermia; perioperative complications; perioperative genomics; pharmacogenomics; precision medicine

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Editor's key points

- Genetic data can help identify patients with comorbidities or increased susceptibility to certain conditions, which might impact their anaesthetic and perioperative course.
- The authors determined the feasibility of identifying patients with genetic susceptibility to anaesthetic complications using an open-source script designed for clinician use.
- The application was validated in a retrospective analysis of a large cohort of patients for three conditions with well-characterised genetic inheritance.
- A strong association between genotype and phenotypes derived from the EHR was verified, but not all genetic susceptibilities were documented in the EHR.
- Patients at high risk for complications often had no documented family history or clinical features of the disease, validating the approach for possible use in clinical decision support.

Relatively straightforward analyses of available genetic data can identify patients with pathologies that might directly impact the anaesthetic and perioperative course. Advances in genetic sequencing have greatly reduced the costs incurred in collecting raw genetic data.[1] An estimated 30 million patients worldwide have genetic information available at the time of surgery, and this number continues to grow.[2,3] Despite this widespread growth, perioperative care providers have limited exposure to genetic data and are not trained to contextualise this information. Existing genetic information, obtained for either clinical or research purposes, can be leveraged to identify patients with genetic susceptibility to conditions that might impact their perioperative care. Furthermore, this information could be incorporated into a clinical decision support system[4] to provide personalised care for patients after their initial enrolment and genotyping. Critical first steps to actualising this potential include incorporating genotype with traditional phenotypes derived from the electronic health record (EHR) and characterising the concordance between these two data types in a representative perioperative population.

Whereas previous studies have been designed to identify genetic variants in patients with a known phenotypic disease[5–9] or in high-risk cohorts,[10–12] our study focused on the opposite, to determine if known gene variants can be used to identify clinically relevant diseases in a generalisable perioperative population. Specifically, to determine if the variants associated with butyrylcholinesterase deficiency, factor V Leiden, and malignant hyperthermia can be used to identify individuals at risk for the associated clinical complications and to determine the proportion of patients who have previously been diagnosed or display clinical findings consistent with each condition. Traditional population estimates have been based on *in vitro* functional studies and not direct genotyping.[13–18] Studies that did perform genotyping have focused on populations selected for clinical evidence of phenotypic disease.[5,6,19–23] Studies in healthy cohorts have been limited to a few thousand individuals, which may not be representative of the surgical population.[10,24–26] Additional information on the genetic basis, inheritance pattern, population frequency, and anaesthetic implications for each of the three studied conditions can be found in the Supplementary Information. Integration of EHR and genetic data enables the concordance between genetic susceptibility and associated diagnoses to be characterised. We hypothesise that patients who may be at increased risk for modifiable perioperative complications can be identified using genetic data obtained as part of their enrolment and that such patients may not have been previously detected based on any relevant EHR-documented diagnoses.

Methods

All study procedures were approved by the University of Michigan Institutional Review Board (HUM00127909 and HUM00099605), and individual informed consent was obtained at the time of enrolment. This article was prepared in accordance with the standards set forth by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.[27] Methods including data collection, outcomes, and statistical analyses were established prospectively and presented at an institutional peer-review committee on April 27, 2017.[28] Because of the sensitive nature of some of the data collected, requests to access the datasets from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

Patient population

Inclusion criteria were all patients enrolled in the Michigan Genomics Initiative (MGI), a longitudinal biorepository within Michigan Medicine, from its inception in 2012–2017. The MGI has integrated genetic data with EHRs on adult patients (≥18 yr) undergoing surgery within Michigan Medicine. Participants were enrolled before surgical procedures.

Genotyping information

The standard genotype format was a dense genotyping chip, or genome-wide association (GWA) data. A subset of our population has additional genetic data available, which were obtained for research purposes unrelated to this current study. This includes 258 individuals with whole exome sequencing (WES) data[29] and 966 individuals with genotypes obtained from single molecule molecular inversion probes (smMIPS). Additional information regarding each of the applied genotyping techniques including coverage and quality control metrics can be found in the Supplementary Information.

Phenotype identification

We developed three EHR-based phenotypes relevant to perioperative care and associated with genetic conditions identifiable within the MGI. Phenotypes were created from data extracted from the EHR using a combination of International Classification of Diseases (ICD) billing diagnoses and search of free-text contained within the preoperative history and physical.[30] The fidelity of each phenotype was then confirmed via limited adjudication by an anaesthesiologist expert (NJD) of the perioperative EHR. First we confirmed our ability to classify ABO blood group using genetics.[31] This functioned as a quality control validation to confirm the appropriate linkage between our genotypic (MGI) and phenotypic (EHR) data. Next we calculated the overall number of patients heterozygous and

homozygous for each of the phenotypes. To confirm association between genotypes identified from the literature and our phenotypes developed from the EHR, we calculated the number of patients in each genetic group positive for the corresponding phenotype. Finally, we performed a manual review of the EHR for homozygous patients to examine for clinical evidence of each condition in the population not carrying a known diagnosis.

ABO blood group identification

We identified genetic variants associated with blood groups and known to have high penetrance.[32] We used three variants and the combinations listed in Supplementary Table S1 to predict ABO blood type. Predictions were then compared with the ABO grouping obtained from preoperative laboratory testing with Cohen's kappa coefficient (κ) between laboratory and genetic determination of blood type, and sensitivity and specificity of each blood group calculated.

Butyrylcholinesterase deficiency

Although more than 65 distinct variants have been linked to butyrylcholinesterase (also known as pseudocholinesterase) deficiency,[33] 80% of the affected population has one of the five most common variants.[7] The first mutation to be characterised, the atypical or *dibucaine-resistant* (A) allele, can classically be confirmed through percent enzymatic inhibition by dibucaine. Other common variants include the *fluoride-resistant* (F1 and F2) alleles, the *silent* (S) allele, and the *Kalow* (K) allele. MGI has three common variants associated with butyrylcholinesterase deficiency that are directly genotyped: A (rs1799807), F1 (rs28933389), and F2 (rs28933390). The EHR-based phenotype, butyrylcholinesterase deficiency, was obtained from a combination of diagnostic codes, a standardised entry in the preoperative anaesthesia history and physical, and free text search for relevant terminology. Within the population homozygous for mutations in the three variants associated with butyrylcholinesterase deficiency, we performed clinical review for evidence of delayed emergence (>30 min from surgical procedure completion to documentation of intact neuromuscular function),[34–36] prolonged intubation (>60 min from completion of surgical procedure to tracheal extubation), or provider-entered text about delayed emergence in patients administered succinylcholine or mivacurium intraoperatively.

Factor V Leiden

Factor V Leiden results from an arginine to glutamine mutation in the *F5* gene (variant rs6025 in the MGI GWA dataset). The EHR-based phenotype, factor V Leiden was obtained from a text search of preoperative history and physical for relevant associated terminology, as an ICD-based diagnosis was complicated by lack of specificity for factor V in the diagnostic code for primary hypercoagulable state. Within the population homozygous for the rs6025 allele X, we performed manual review for clinical evidence of prior thromboembolic disease or hypercoagulability, including pulmonary embolism, deep vein thrombosis (DVT), and atrial thrombus.

Malignant hyperthermia

We developed an EHR-derived phenotype for malignant hyperthermia from diagnostic codes, standardised entry in the preoperative anaesthesia history and physical, and free text query. All patients identified from the automated query were further classified into three categories: (1) confirmed malignant hyperthermia case, (2) suspected clinical presentation, and (3) immediate family history of malignant hyperthermia. The European Malignant Hyperthermia Group (EMHG) has identified 48 mutations in the *RYR1* gene and two mutations in the *CACNA1S* gene to be associated with malignant hyperthermia susceptibility.[37] Preliminary review of MGI GWA data revealed inadequate coverage within our GWA data (single nucleotide polymorphisms [SNPs] assessed are listed in Supplementary Table S2). We therefore assessed the prevalence of mutations associated with malignant hyperthermia in the population with WES (n=258) or smMIPS (n=966) genotype data for which we had sufficient genetic coverage. Specific mutations assessed in our WES and smMIPS population are listed in Supplementary Table S2. We scored other mutations in the *RYR1* gene as described,[38,39] then cross-referenced for potential significance with an annotation provided by the Laboratory for Molecular Medicine (Partners HealthCare Personalized Medicine, Boston, MA, USA) as detailed in the Supplementary Information. We performed clinician review for evidence of malignant hyperthermia in the population with mutations deemed pathogenic (EMHG list) or other mutations in the *RYR1* gene (based upon bioinformatic scoring plus variant annotation).

Application for clinician use

Based upon the strong associations between genotype and both EHR-derived phenotypes and clinical evidence of complications, we provide a script to annotate patients and their genetic susceptibility. The script takes a standard variant call format (vcf) file and a provided set of genetic annotations that we used in the manuscript. The script outputs all samples within the vcf file that have either homozygous or heterozygous mutations associated with increased susceptibility to butyrylcholinesterase deficiency, factor V Leiden, or malignant hyperthermia. The script (included in the Supplementary Information) is open source, posted on Zenodo (https://doi.org/10.5281/zenodo.3931690), and linked to this manuscript's digital object identifier (DOI).

Results

The MGI population at the time of initial data analysis included integrated GWA data and EHR records on 40 769 patients. Whole exome sequence data were available on 258 patients, and smMIPS data were available on 966 patients. The overall population had a median age of 55 yr (inter-quartile range [IQR], 42–66); 54% were female, and 89% were Caucasian (self-reported race). Additional descriptive characteristics of the MGI population are shown in Table 1.

ABO blood group

ABO blood group was available on 5799 patients (14.2% of the total MGI population). Cohen's kappa coefficient (κ) between laboratory and genetic determination of blood type was 0.944. Genotype was observed to predict blood type with high sensitivity and specificity (Tables 2 and 3). Our application

Table 1 Patient and procedural characteristics of the Michigan Genomics Initiative population. Median BMI was 28 (inter-quartile range, 24–33); 16% were current smokers and 29% were former tobacco users; 46% were classified as ASA 2 and 41% as ASA 3 (during the procedure with the highest/maximum ASA physical status classification).[48] COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; EHR, electronic health record; Max, maximum.

		Median	IQR	Count (n=40 769)	%
Sex					
Male				18 933	46.4
Female				21 836	53.6
Age (yr)		55	42–66		
Ethnicity					
Asian				601	1.5
Caucasian				36 407	89.3
Black/African				2043	5.0
Hispanic				394	1.0
Middle Eastern				8	0.0
Native American/Pacific Islander				178	0.4
Multi-racial				13	0.0
Other/unknown/declined				1125	2.8
Height (cm)		170.2	162.6–177.8		
Weight (kg)		84.0	70.6–99.5		
BMI (kg m^{-2})		28	24–33		
ASA physical status (Max)					
1				3299	8.1
2				18 654	45.8
3				16 839	41.3
4				1931	4.7
5				35	0.1
6				1	0.0
Unknown/missing				10	0.0
Tobacco use					
Non-smoker				21 914	53.8
Former smoker				11 766	28.9
Current smoker				6685	16.4
Unknown/missing/conflicting				404	1.0
Alcohol abuse				546	1.3
Cerebrovascular disease				2641	6.5
Malignant hyperthermia					
Clinical diagnosis				7	0.0
Immediate family history				8	0.0
Butyrylcholinesterase deficiency	*Documented diagnosis*			42	0.1
Ischaemic heart disease				2790	6.8
Asthma or COPD				6457	15.8
Diabetes mellitus	None			34 719	85.2
	Diet/exercise/lifestyle modification			889	2.2
	Oral hypoglycaemic medications			2893	7.1
	Insulin			2267	5.6
	Unknown/missing/conflicting			1	0.0
Factor V Leiden	*Documented diagnosis*			262	0.6
Deep venous thrombosis				2215	5.4
Renal failure				3071	7.5
Postoperative nausea/vomiting				6058	14.9

flags any patient whose laboratory and genetically predicted blood type does not match from subsequent predictions in order to alert the user of a potentially incorrect linkage between patient genotype and EHR.

Butyrylcholinesterase deficiency

Analysis of genetic data revealed 25 of 40 769 (0.1%) patients were homozygous and 1918 (4.7%) were heterozygous for mutations associated with butyrylcholinesterase deficiency. Of the 25 homozygous patients, 23 were positive for the *atypical* (A) genotype, 0 were positive for the fluoride-resistant 1 (F1) genotype, and two were positive for the fluoride-resistant 2 (F2) genotype. The overall allele frequency was 0.0181 for the A genotype, 0.0009 for the F1 phenotype, and 0.0052 for the F2 phenotype. The carrier rate was 3.5%, 0.2%, and 1.0%, respectively. Of the 25 homozygous individuals, 14 (56.0%) carried a pre-existing diagnosis, based upon our automated EHR-derived clinical phenotype, compared with nine (0.5%) of the 1918 heterozygous individuals, and 19 (0.05%) of the 38 826 wild-type individuals. A clinician review of the 25 homozygous patients found 13 had been exposed to succinylcholine previously. All 13 of those exposed individuals had clinical evidence of either delayed emergence or prolonged intubation on clinician review. The remaining 12 individuals had no prior record of succinylcholine exposure. Full results can be seen in Table 4.

Table 2 Sensitivity and specificity of ABO blood group prediction using genotype: counts and percentage of total for each blood type. EHR, electronic health record.

Laboratory blood type (EHR)	Count	%
A	2339	40.3
B	693	12.0
AB	239	4.1
O	2528	43.6
Total	5799	100.0

Table 3 Sensitivity and specificity of ABO blood group prediction using genotype: sensitivity and specificity of genetic testing for predicting each blood type.

Blood type prediction (genetics)	Sensitivity	Specificity
A	99.62	95.14
B	96.25	99.80
AB	99.58	99.55
O	93.28	99.91

Factor V Leiden

With 29 individuals (0.07%) homozygous and 2153 (5.3%) heterozygous for factor V Leiden mutation, the overall allele frequency was 0.0271. Of the 29 homozygous individuals, 3 (10.3%) carried a pre-existing factor V Leiden diagnosis ($P<0.001$, compared using χ^2 test to the 52 [0.1%] out of 38 587 wild-type individuals) based upon our automated EHR-derived clinical phenotype. Of the 2153 heterozygous individuals, 207 (9.6%) carried a factor V Leiden diagnosis ($P<0.001$). Clinician review identified thromboembolic complications in 6 (20.7%) of patients homozygous for factor V Leiden mutation. Using ICD codes, 4 (13.8%) of 29 homozygous individuals, 220 (10.2%) of 2153 heterozygous, and 1991 (5.2%) of 38 587 wild-type individuals were positive for prior DVT based upon diagnostic codes.

Malignant hyperthermia

Susceptibility to malignant hyperthermia was assessed in the 258 patients with WES data and 966 patients with smMIPS data. Within these patients, we detected two mutations pathogenic for malignant hyperthermia susceptibility (c.1841G>T and c.7300G>A). A clinician review of these two individuals revealed no clinical history associated with mutations in the *RYR1* gene, including central core disease, congenital fibre type disproportion, multiminicore disease, centronuclear myopathy, King–Denborough syndrome, or rhabdomyolysis.[40] Both individuals with genetic susceptibility to malignant hyperthermia had been previously exposed to a triggering anaesthetic. Bioinformatic scoring also detected two individuals with other mutations in the *RYR1* gene (c.1441-2A>G and c.631+1G>T). The c.1441-2A>G and c.631+1G>T variants in *RYR1* occur within the canonical splice site (~1,2) and are predicted to cause altered splicing leading to abnormal or absent ryanodine receptor 1 protein. Neither variant has been previously reported in individuals with disease, although the c.631+1G>T variant was identified in 2 of 9996 Ashkenazi Jewish chromosomes in The Genome Aggregation Database (gnomAD).[41] The bi-allelic loss of function of the *RYR1* gene is an established mechanism for autosomal recessive congenital myopathy/central core disease but not malignant hyperthermia susceptibility. A clinician review of these patients showed no relevant clinical history. Within the 40 769 individual MGI population, we found three cases of confirmed malignant hyperthermia, seven cases of suspected clinical presentation, and eight individuals with immediate family history of malignant hyperthermia (Table 4).

Discussion

In a large cohort of surgical patients, we validated the strong association between genotype and known diagnosis of butyrylcholinesterase deficiency and factor V Leiden and clinical evidence of complications associated with these processes. In addition, we identified the presence of patients likely to be susceptible to preventable complications with a future anaesthetic who had no prior evidence of susceptibility (11 individuals homozygous for butyrylcholinesterase deficiency, 23 individuals homozygous for factor V Leiden, two individuals heterozygous for pathogenic malignant hyperthermia mutations, and two individuals heterozygous for other *RYR1* mutations). We report the frequency of three common variants associated with butyrylcholinesterase deficiency and factor V Leiden mutations in a 40 769 patient surgical population.

Our study builds on existing literature by integrating patient genotype with EHR data. This lays the framework for future precision-medicine-based clinical decision support systems by creating a clinical application to identify patients with susceptibility to perioperative complications using genotype. We selected conditions with Mendelian inheritance and modifiable risk profiles; however, future studies might focus on complications with more complex genetic associations, such as myocardial injury after noncardiac surgery[42] or postoperative nausea and vomiting.

Concordance with expected results

The high agreement between ABO blood type and genetic prediction phenotype confirms excellent linkage between genotype and EHR data. The less-than-perfect agreement may be a result of gene variants not included in our prediction or diseases that affect AB antigen appearance.[43] We found a slightly higher than expected prevalence of both homozygosity and heterozygosity for butyrylcholinesterase deficiency (0.06% compared with 0.02–0.03% and 4.7% compared with 2.0–4.0%, respectively).[33] This probably relates to either true differences in prevalence in local populations or to random differences based on small sample sizes. The frequency of patients homozygous for factor V Leiden in the MGI population is higher than expected (0.07% compared with 0.02%), and the frequency of heterozygous patients is as expected in a population primary comprised of white Americans (5.3% compared with 5.2%).[44] The slightly higher than expected rate of homozygotes may relate to Michigan Medicine being a referral centre for patients with factor V Leiden and its complications leading to a slight oversampling of these patients. The hazard ratios for developing DVT in our population (heterozygous, 1.9;

Table 4 Summary of genetic analysis. Because the malignant hyperthermia group was deliberately selected to verify our ability to detect pathogenicity, this cohort should be viewed as not representative of the general population, and carrier frequency non-informative. A, adenine; AV, Atypical variant; c., coding DNA; DVT, deep vein thrombosis; EHR, electronic health record; F1, fluoride-resistant type 1 variant; F2, fluoride-resistant type 2 variant; G, guanine, T, thymine.

Genotype			*n*	%	EHR phenotype	%	EHR phenotype (DVT)	%	Clinical evidence	%	Allele frequency
Butyrylcholinesterase deficiency (*n*=40769)	Atypical (rs1799807)	Wild-type	39320	96.4	21	0.1					0.0181
		Heterozygous	1426	3.5	7	0.5					
		Homozygous	23	0.1	14	60.9			13	56.5	
	F1 (rs28933389)	Wild-type	40694	99.8	41	0.1					0.0009
		Heterozygous	75	0.2	1	1.3					
		Homozygous	0	0.0	0	0.0			0	0	
	F2 (rs28933390)	Wild-type	40350	99.0	41	0.1					0.0052
		Heterozygous	417	1.0	1	0.2					
		Homozygous	2	0.0	0	0.0			0	0	
Butyrylcholinesterase deficiency (Total) (*n*=40769)		Wild-type	38826	95.2	19	0.0					0.0241
		Heterozygous	1918	4.7	9	0.5					
		Homozygous	25	0.1	14	56.0			13	52.0	
Factor V Leiden (*n*=40769)	(rs6025)	Wild-type	38587	94.6	52	0.1	1991	5.2			0.0271
		Heterozygous	2153	5.3	207	9.6	220	10.2			
		Homozygous	29	0.1	3	10.3	4	13.8	6	20.7	
Malignant hyperthermia (*n*=1224)	c.1841G>T (rs193922772)	Heterozygous	1	0.1	0	0.0			3 (confirmed)	0.0	0.3268 *
	c.7300G>A (rs121918593)	Heterozygous	1	0.1	0	0.0			7 (suspected/clinical)	0.0	
	c.1441-2A>G	Heterozygous	1	0.1	0	0.0			8 (family history)	0.0	
	c.631+1G>T	Heterozygous	1	0.1	0	0.0					

homozygous, 2.7) were lower than those found in a large cohort study (heterozygous, 2.4; homozygous, 22.0),[25] which is likely a combination of length of surveillance and baseline population risk. We compared allelic frequencies between our population and the gnomAD in Supplementary Table S3.[41] Frequency discrepancies may also result from differences between the surgical population recruited for our study and estimates from healthy controls. Because the malignant hyperthermia group was deliberately selected to verify our ability to detect pathogenicity, this cohort should be viewed as not representative of the general population, and carrier frequency should not be extrapolated.

Methodologic strengths and weaknesses

The notable strengths of the study include the large number of perioperative patients with genetic data available for analysis and linkage with EHR-derived data including ICD codes, anaesthetic records, and history and physical documentation. Another strength is that the four major variants (rs6025, rs1799807, rs28933389, rs28933390) were all directly genotyped in our customised Illumina Infinium platform, eliminating sources of error secondary to imputation.

A major limitation is that this is a single-centre study without external validation. As a retrospective analysis, we cannot use the results of genetic testing to make future clinical diagnoses; however, the strength of the associations with our curated phenotypes justifies research into how providers might alter their care in response to this information. Another limitation is the variable penetrance of our phenotypes. Specifically, most people with genetic susceptibility to malignant hyperthermia will not display clinical manifestations of a hypermetabolic crisis when exposed to triggering agents.[40] Another limitation is that the very low frequency of the selected conditions limits the economic feasibility of prospective genetic testing. Notably, the American College of Medical Genetics Consensus Statement on Factor V Leiden Mutation Testing recommends factor V Leiden testing only in patients with increased risk profile based upon personal or family history of venous thromboembolic events at an early age.[45] We are not advocating for additional perioperative genetic testing to assess for these low frequency events, only providing analysis and risk stratification using genetic testing that has already been performed for research or unrelated clinical purposes. Furthermore, this methodology can be applied to higher frequency complications, which have more complex genetic associations.[46–48]

Source data for EHR-based phenotypes have important limitations, which we have recognized in this study. Depending on EHR documentation practices, documented diagnoses may have imperfect sensitivity or specificity for detecting a 'gold standard' for a particular phenotype (i.e. diagnosis of the disease in the case where all diagnostic testing was available and performed). Similarly, EHR manifestations of a diagnosis may also have imperfect discrimination. To address these limitations, we importantly derived two separate phenotypes from the EHR for both factor V Leiden and butyrylcholinesterase deficiency. Initial phenotypes are based on a documented diagnosis of the condition (specifically, factor V Leiden and butyrylcholinesterase deficiency). Secondary phenotypes assess for clinical manifestations of the genetic condition (thromboembolic disease or hypercoagulability and delayed emergence or prolonged intubation, respectively).

Our research raises important ethical considerations and privacy concerns. Additional IRB approval and informed consent would need to be obtained before incorporating our application in future prospective studies which might alter patient care and perioperative outcomes. Furthermore, no

consensus exists regarding best practice for returning incidental genomic research results to the individual participants.[49] A final limitation is that our study contains coverage for a limited number of genetic variants, and not every variant associated with each condition has been characterised. Therefore, although our study is helpful at identifying patients likely to be at increased risk, genotype should *not* be used to lower risk stratification.

Conclusions

As genetic testing becomes more common, it may be possible to leverage genetic data to improve existing prediction models for perioperative complications in selected surgical patient populations and prevent or diminish the impact of these complications via modifications to anaesthetic care. We demonstrate the feasibility of identifying patients with genetic susceptibility to perioperative complications using an application designed for clinicians that we are making freely available. We validated this application in a retrospective analysis using three conditions with well-characterised genetic inheritance. Our analysis verified strong associations between genotype and phenotypes derived from the EHR. In addition, we show that patients at high risk for complications often have no documented family history and have never displayed clinical features of the disease process. Future studies are necessary to expand an understanding of complications potentially associated with more complex genetic inheritance and integrate our genetic analysis into clinical decision-support systems.

Authors' contributions

Conception and design: NJD, SK, ME, MM, GM, CBD
Acquisition of data: NJD, SK, WH, CW
Analysis of data: all authors
Drafting the article: NJD, ME, MM, WH, CBD
Clinician review of phenotypes: NJD
Development of software application: NJD, CBD
Critical revision of the article: all authors
All authors approved the final version to be published and agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declarations of interest

NJD, SK, ME, MM, GM, WEH, CJW have no conflicts of interest to disclose. CD is a paid consultant for Thrive Earlier Detection. He is also an inventor on various technologies unrelated to the work described in this manuscript. Some of the licenses are or will be associated with equity or royalty payments. The terms of all these arrangements are being managed by Johns Hopkins University in accordance with its conflict of interest policies.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.08.009.

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