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The use of a systematic review to verify the completeness of the PharmGKB database based on the search for genetic variant related side effects during ovarian cancer treatment with platinum compounds

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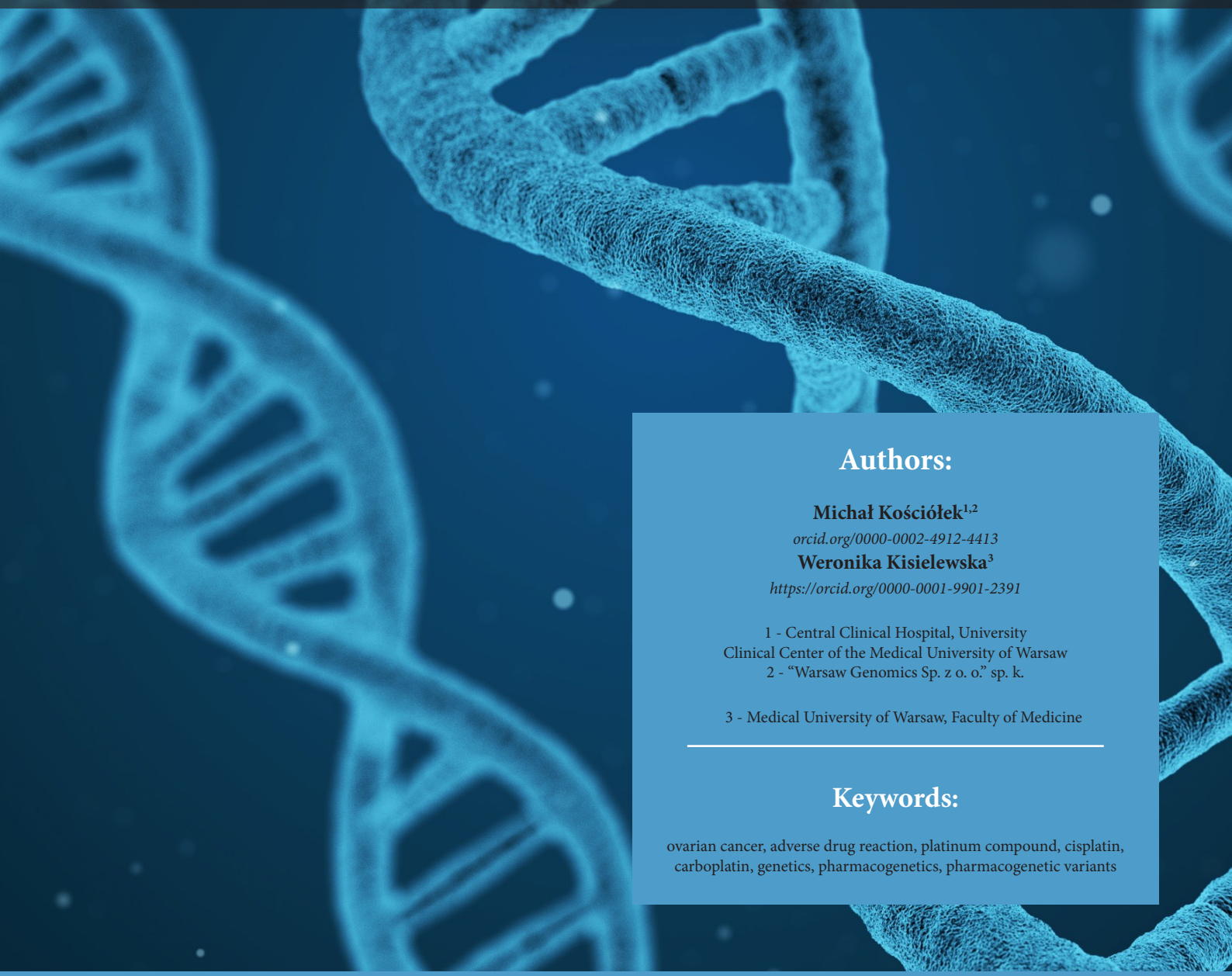

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Abstract

Introduction

PharmGKB (The Pharmacogenomics Knowledgebase) contains information on the correlation between genetic variability and response to pharmacotherapy. The authors of PharmGKB indicate that the database does not include all the knowledge gathered in PubMed. This paper aimed to obtain variants from the PharmGKB and determine whether additional variants related to adverse drug reactions (ADR) during the treatment of ovarian cancer with platinum compounds have been discovered to verify PharmGKB completeness. For this purpose, a systematic review was carried out.

Methods

First, all variants related to ADR risk in patients with ovarian cancer treated with platinum compounds (in monotherapy or with paclitaxel or docetaxel) were identified in the PharmGKB. In the second stage, a systematic search of PubMed and Embase was carried out to identify variants not indexed in the PharmGKB and thus verify its completeness.

Results

As a result of the systematic review, three publications describing four new variants were found, which completed the pool of 10 variants found in PharmGKB. A correlation between rs363717, rs12762549 and a reduction in the odds of grade III-IV anaemia was described in publications. Variant rs1695 reduced the odds of grade I–IV thrombocytopenia and grade III-IV anaemia and increased the odds of grade II anaemia. Rs11615 was proved to be associated with an increased odds of grade III-IV anaemia.

Conclusion

In the search for pharmacogenetic data, until the introduction of fully automated indexing in the PharmGKB, a systematic review should be performed.

Introduction

The knowledge about the influence of genes on treatment – pharmacogenomics, is becoming the subject of interest for different medical specialities. Information on pharmacogenomics is published in numerous journals, increasingly not directly related to genetics. This situation makes the development of databases indexing individual publications on this topic necessary.

Genotype variability, translating into different metabolism and action of some drugs, is based on the difference in DNA nucleotide sequences of two origins: recombination during impregnation and mutations. A mutation is a change in genetic material resulting from an error or damage not corrected by the cell's repair mechanisms have not corrected.[1] A nucleotide change at a specific gene locus is called a variant. Each variant is tagged with a unique dbSNP reference number representing precise information about the position, gene, and nature of the change occurring.[2]

The Pharmacogenomics Knowledgebase (PharmGKB) is an online database funded by the National Institutes of Health.[3] It collects information on the association of genetic variety with response to pharmacotherapy. The data are publicly available and originates from the literature collected through the PubMed search. Articles are manually selected. Interpretation and clinical significance assessment are performed by curators.[4] The authors describing this process indicate that PharmGKB does not include all the pharmacogenetic knowledge in PubMed, and the current data acquisition process requires automation.[5] A fully systematic search of medical information databases can contribute to the identification of new genetic variants related to the response to the treatments and indirectly verify the completeness of the PharmGKB database.

This paper aimed to obtain variants from the PharmGKB and determine whether additional variants related to side effects (adverse drug reaction, ADR) during the treatment of ovarian cancer with platinum compounds have been discovered to verify PharmGKB completeness. For this purpose, a systematic review was carried out. This publication was based on the results of the master thesis by Kościółek M. entitled "The validity of the genetic diagnostics qualification to the treatment of ovarian cancer in Poland in the prevention of side effects in patients with the planned inclusion of platinum compounds".[6] The results of selected thesis chapters have been published in this article.

Methods

In the first stage, all genetic variants responsible for modifying ADR risk in patients with ovarian cancer treated with platinum compounds in monotherapy or combined with paclitaxel or docetaxel were identified in the PharmGKB database. The search query "Platinium compounds" in PharmGKB was used, and ADR-related variants for platinum compound treatment were identified on the Clinical Annotations page. Variants with the clinical significance level – from 1A (high) to 3 (low)[7] associated with the ADR for treatment containing platinum compounds were distinguished. The "toxicity" filter was used in the "type" column, and the "ovarian neoplasms" filter was used in the "phenotype" column. The obtained data were planned to be compared with the systematic review results, making it possible to identify additional data.

Subsequently, PubMed and Embase databases were searched to identify variants not indexed in PharmGKB, to verify its completeness. Publications meeting the following PICOS criteria were included in the review:

- Patients with ovarian cancer who have undergone genetic testing.
- Treatment with cisplatin, carboplatin, oxaliplatin intravenously or intraperitoneally as monotherapy or with paclitaxel/docetaxel.
- Outcome: occurrence of an adverse drug reaction.
- Study: full-text publications assessing the effect of genes or variants on the incidence of ADR of platinum treatment.

The following publications were excluded from the review:

- number of patients <10 persons,
- describing only the association of a gene with side effects, without indicating a specific variant,
- describing only variants in genes involved in taxane metabolism (based on Marsh et al.[8] and Oshiro et al.[9]),
- publications indexed and described in the PharmGKB,
- publications in languages other than English and Polish.

The scope of the search was determined between 01/02/2010 and 18/02/2021.

Search strategy

The search strategy used in the systematic review was based on keywords related to:

- tumours and the ovary,
- general phrases related to genetics, pharmacogenetics, mutations and variants, supplemented with the keywords related to genes and variants with confirmed effects on treatment with platinum compounds in the PharmGKB database (connected by the Boolean "OR" operator),
- platinum compounds, detailing individual drugs,
- phrases related to ADR, toxicity and metabolism,

The search strategy was included in the supplement (Table 5 and Table 6).

Selection of studies

Primary and secondary studies found in PubMed and Embase were imported into EndNote X9.[10] The selection process based on titles and abstracts was made in Microsoft Excel.[11] The final qualification was based on the full-text assessment. A single researcher carried out the process of searching, selecting, extracting and analysing the results due to the necessity to meet the requirements of the master thesis.

Data extraction and management

A single researcher carried out the extraction process using a structured form. The following data were extracted from the publication:

- the number of persons undergoing the genotyping process together with information on the treatment regimen used,
- variant and gene,
- the adverse reaction assessed with the severity and scale used in the assessment,
- alleles, genotype or genotypes assessed as a comparison with the model used to calculate odds ratio (OR),
- OR with the lower and upper confidence interval and the value of the p-value (for corrected values, if available).

Quality assessment

No appropriate scale was found to assess publications that would meet the goals and needs of this study. For this reason, the detailed characterisation of each included study was presented in a descriptive form, taking into account two aspects: 1) correct presentation of changes occurring in DNA, represented by a variant with a possibility of distinguishing the reference genotype (reference homozygote) from alternative hetero- and homozygotes in the publication, 2) including information on the model of calculating OR for the studied genotype (e.g. dominant, recessive, additive model). Including information

on the method of calculating OR enables the assessment of the influence of individual alleles on the endpoint.[12]

Assessment of the completeness of the PharmGKB

The completeness assessment was carried out by verifying whether the studies of works included in the systematic review were found in the built-in PharmGKB search engine. The publications found in PharmGKB were tabulated with new publications found as part of the systematic review, along with their brief characteristics. Publications not indexed in the database were subjected to a detailed qualitative assessment and analysis of the results. In this work, the description of non-indexed publications has been simplified. The complete analysis is included in the content of the master's thesis.

Qualitative analysis of the results of non-indexed studies

Due to the insufficient number of the same variants analysed in the pool of selected studies, the accumulation of results was not carried out.

All variants correlated with the occurrence of ADRs were qualified for analysis. In a descriptive form, information on the applied genetic models in the calculation of OR was provided. The interpretation of OR – influence of allele/alleles or genotype/genotypes on the chance of ADR, was presented in a descriptive and tabular form. Data were presented for corrected values. The variants included in the review were adjusted to the standards compliant with the dbSNP database.[13] According to the dbSNP database methodology, all the genes on the minus strand should be mapped to the plus strand and the records of variants on the minus strand shown as complementary nucleotides mapped to the plus strand (A-T or G-C). The dbSNP also defines the variant considered the reference and the alternative variant, which was implemented in the qualitative analysis.

Results

Results of the search

The search results for variants related to ADRs in the PharmGKB and reasons for exclusion from the further analysis were presented in Table 1. 22 records were found, and 10 ouf ot 22 variants were included in the further analysis. Nine records were excluded due to improper treatment type or intervention in a population not eligible for review (e.g. study group included patients who have cancer of another organ) and three records referred to genes closely involved in taxane metabolism.

As a result of the search in Pubmed and Embase, 359 and 1099 publications were found, respectively. For further analysis, 116 publications were selected based on the full texts. 34 additional publications were obtained from references. Five publications were included in the review. The selection of publications included in the review was presented in Diagram 1.

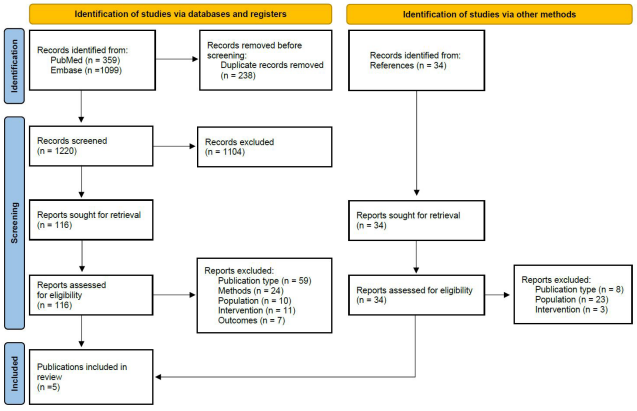

Diagram 1. PRISMA 2020 flow diagram for new systematic reviews.

Assessment of completeness and systematic character of the PharmGKB

In the PharmGKB search engine, it was checked whether the qualified publications were indexed in the database. The results of the search are presented in Table 2. Three publications were qualified for further detailed analysis. PharmGKB curators have already analysed the remaining two publications indexed in the PharmGKB, and the results of these analyses are included in the database and are available online.[15, 16]

Lambrechts et al., Liblab et al. and Ferracini et al. studies were not found in the PharmGKB. Additionally, when searching the PharmGKB for variants analysed in the publications, two variants described in Lambrechts et al. were not found: rs363717 and rs12762549.

Description of studies

Table 3 presents the qualified publications. In all studies, patients were treated with carboplatin either as monotherapy or with docetaxel or paclitaxel. The results of five qualified publications were based on the analysis of samples from four patient populations. In He et al.[21] and McWhinney-Glass et al.[17] the analysed samples were from a single randomised phase III clinical trial (The Scottish Randomized Trial in Ovarian Cancer, SCOTROC1). Adverse reactions were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) 2.0, 4.03, or 5.0. The summary of statistically significant results was presented in Table 4.

Lambrechts et al.

The study was conducted on 50 women treated with car-

Table 1. Variants correlated with the occurrence of ADRs during the treatment with platinum compounds found in PharmGKB.

Variant	Gene	Drug	Reason for exclusion		Eligible for analysis
			Incompatible population or intervention	Taxane metabolism only	
rs2032582 (A>C)	ABCB1	Platinum compounds; Taxanes	–	Yes	No
rs2032582 (A>T)	ABCB1	Platinum compounds; Taxanes	–	Yes	No
rs1061472	ATP7B	Carboplatin; Taxanes	–	–	Yes
rs1801249	ATP7B	Carboplatin; Taxanes	–	–	Yes
rs2849380	BCL2	Carboplatin; Docetaxel; Paclitaxel	–	–	Yes
rs2070676	CYP2E1	Cisplatin; Cyclophosphamide	Yes		No
CYP3A5*1; CYP3A5*3	CYP3A5	Carboplatin; Paclitaxel	–	Yes	No
rs1051740	EPHX1	Cisplatin; Cyclophosphamide	Yes	–	No
rs11615	ERCC1	Cisplatin; Cyclophosphamide	Yes	–	No
rs3594	GSR	Carboplatin; Taxanes	–	–	Yes
rs3957357	GSTA1	Cisplatin; Cyclophosphamide	Yes	–	No
rs1799735	GSTM3	Cisplatin; Cyclophosphamide	Yes	–	No
rs1695	GSTP1	Cisplatin; Oxaliplatin; Platinum compounds	Yes	–	No
rs1052536	LIG3	Cisplatin; Cyclophosphamide	Yes	–	No
rs3219484	MUTYH	Cisplatin; Cyclophosphamide	Yes	–	No
rs1801280	NAT2	Cisplatin; Cyclophosphamide	Yes	–	No
rs544093	OPRM1	Carboplatin; Docetaxel; Paclitaxel	–	–	Yes
rs9825762	SCN10A	Carboplatin; Taxanes	–	–	Yes
rs139887	SOX10	Carboplatin; Docetaxel; Paclitaxel	–	–	Yes
rs879825	VEGFA	Carboplatin; Taxanes	–	–	Yes
rs6900017	VEGFA	Carboplatin; Taxanes	–	–	Yes
rs879207	–	Carboplatin; Docetaxel; Paclitaxel	–	–	Yes

Table 2. Publications indexed in the PharmGKB.

Author, year, reference	Variant	Journal	Impact factor (year)	PharmGKB status
McWhinney-Glass et al., 2013 [17]	rs2849380, rs544093, rs139887, rs879207	Clinical Cancer Research	10.107 (2019) [18]	Indexed
Lambrechts et al., 2015 [19]	rs363717*, rs12762549*, rs11615	BMC Pharmacology and Toxicology	1.771 (2019) [20]	Not found
He et al., 2016 [21]	rs1061472, rs1801249, rs3594, rs9825762, rs6900017, rs879825, rs9369421	Pharmacogenomics Journal	2.910 (2019) [22]	Indexed
Liblab et al., 2020 [23]	rs1695	Asian Pacific Journal of Cancer Prevention	2.514 (2014) [24]	Not found
Ferracini et al., 2020 [25]	rs1695	Clinical and Translational Science	3.373 (2019) [26]	Not found

* Variants not found in the PharmGKB

Table 3. Characteristics of included studies.

Author	Gene	Variant	N	Intervention	Outcome	CTCAE scale
McWhinney-Glass et al.	BCL2	rs2849380	808	Carboplatin + paclitaxel (n = 400) Carboplatin + docetaxel (n = 408)	Grade II-IV neurotoxicity	2.0
	OPRM1	rs544093				
	SOX10	rs139887				
	TRPV1	rs879207				
Lambrechts et al.	ABCA1	rs363717	290	Carboplatin (n = 50) Carboplatin + paclitaxel (n = 240)	Grade III-IV anaemia	4.0
	ABCC2 rs12762549					
	ERCC1	rs11615				
He et al.	ATP7B	rs1061472	808	Carboplatin + paclitaxel (n = 400) Carboplatin + docetaxel (n = 408)	Grade III-IV gastrointestinal toxicity	2.0
		rs1801249				
	GSR	rs3594				
	SCN10A	rs9825762				
	VEGFA	rs6900017				
		rs879825				
		rs9369421				
Liblab et al.	GSTP1	rs1695	52	Carboplatin (n = 3) Carboplatin + paclitaxel (n = 49)	Grade II anaemia	4.03
Ferracini et al.	GSTP1	rs1695	112	Carboplatin (n = 1) Carboplatin + paclitaxel (n = 111)	Grade III-IV anaemia	5.0
					Grade I-IV Thrombocytopenia	

boplatin and 240 women treated with carboplatin with paclitaxel. The authors presented three variants related to the metabolism of platinum compounds and their association with ADR: rs11615 (*ERCC1*), rs363717 (*ABCA1*) and rs12762549 (*ABCC2*). Due to the known influence of genes *ABCB1* and *CYP3A4* on taxane metabolism, the variants rs1128503 and rs4986910 were not eligible for review.

Hematopoietic and nervous system toxicity was analysed using the CTCAE 4.0 scale. The study proved a correlation between the assessed variants and the incidence of grade III-IV anaemia. For a variant of the gene related to taxane metabolism, a correlation for grade III-IV thrombocytopenia was proven.

Researchers incorrectly indicated the reference and alternative alleles for the rs363717 variant. [27] The other descriptions of the variants were provided without errors. In the publication, the researchers adopted an additive model to calculate OR. Assessment of increased or decreased risk between individual genotypes depending on the presence of a single alternative allele was possible.

The G allele in the rs12762549 C>G (*ABCC2*) was associated with a lower chance of grade III-IV anaemia (OR = 0.51, 95% CI: 0.33–0.81, p = 0.004). In order to adapt the notation of rs11615 and rs363717 to dbSNP standards, the notation was mapped to the plus strand. Additionally, in rs363717, the nomenclature of the alternative to reference allele and the reference to alternative genotype was reversed, and the conversion was performed by inverting the OR and the confidence interval. As a result of these actions, it can be concluded that the G allele in rs11615 A>G (*ERCC1*) was associated with a higher chance of grade III-IV anaemia (OR = 1.61, 95% CI: 1.04–2.50, p = 0.031) and TT genotype in rs363717 C>T (*ABCA1*) was associated with a lower chance of grade III-IV anaemia (OR = 0.48, 95% CI: 0.31–0.76, p = 0.002).

Liblab et al.

The study was conducted on three women treated with carboplatin and 49 women treated with carboplatin plus paclitaxel. The authors presented three variants related to the metabolism of platinum compounds: rs1695 (*GSTP1*), rs25487 (*XRCC1*) and rs3212986 (*ERCC1*).

Haematopoietic toxicity (anaemia, neutropenia, thrombocytopenia) was analysed on the CTCAE 4.03 scale. The study indicated a statistically significant correlation between the rs1695 variant and the incidence of grade II anaemia. According to the data included in the study, anaemia more severe than grade II was not identified.

In the publication, variants in the genes located on the minus strand were described inconsistently. In the ERCC1 gene, the record was mapped to the plus strand. In the XRCC1 gene, the description of the variant was presented on the minus strand. Researchers presented reference and alternative alleles for the rs25487 variant inconsistently with the dbSNP standard - in terms of

frequency of occurrence and not the accepted notation for this variant.[27] It was possible to make the necessary transformations to the dbSNP standard.

The authors did not have to implement a genetic model to calculate the effect of individual alleles on the chance of ADRs because only two genotypes were detected for a statistically significant variant in the study population.

The authors demonstrated a statistically significant effect of the AG genotype in the rs1695 A>G (*GSTP1*) on the increased chance of grade II anaemia compared to the AA homozygote (OR = 5.2, 95% CI: 1.000–27.146, p = 0.036). The results for the remaining variants were statistically insignificant.

Ferracini et al.

The study was conducted in 111 women treated with carboplatin plus paclitaxel and one woman treated with carboplatin. The authors presented the rs1695 (*GSTP1*) variant related to the metabolism of platinum compounds. The other three variants: rs1045642, rs1128503, rs2032582 in the *ABCB1* gene, were not qualified for review due to the known effect of this gene on taxane metabolism.

Toxicity to the haematopoietic system (anaemia, neutropenia, thrombocytopenia) and the nervous system was analysed on the CTCAE 5.0 scale. The authors proved a correlation between the assessed variant and the incidence of grade III-IV anaemia and grade I-IV thrombocytopenia. A correlation was also proven between the rs1045642 and grade II-IV neurotoxicity in the *ABCB1* gene related to taxane metabolism.

The variants were presented correctly, making it possible to determine which alleles can be considered reference and alternative. For the calculation of OR, the results for both the dominant and recessive models were presented, which enabled the assessment of ADR risk depending on the genotype.

In the multivariate analysis for the rs1695 A>G (*GSTP1*), the researchers proved a lower chance of grade III-IV anaemia for AG heterozygotes (OR = 0.16, 95% CI: 0.03–0.84, p = 0.03) compared to AA homozygotes and a similar correlation for the dominant model – the sum of two genotypes AG + GG (OR = 0.17, 0.04–0.69, p = 0.01) versus AA homozygotes.

The authors proved that having an AG genotype in comparison to AA homozygotes and having a GG genotype in comparison to AA homozygotes was associated with a reduction in the chance of grade I-IV thrombocytopenia (OR = 0.32, 95% CI: 0.12–0.82, p = 0.01 and OR = 0.11, 95% CI: 0.02–0.59, p <0.01). Similar associations were confirmed for the dominant model – AG + GG genotypes versus AA homozygotes (OR = 0.27, 95% CI: 0.12–0.64, p <0.01) and the recessive model – GG genotype versus AG + AA genotypes (OR = 0.18, 95% CI: 0.03–0.85, p = 0.03).

The possibility of 1. presenting statistically significant ORs for both ADRs (anaemia and thrombocytopenia) using the same models and 2. the ease of assessing the chance of ADR occurrence for this model in further discussions and conclusions (a single OR can describe ADRs chance for alternative homo- and heterozygotes) were the reasons why only the results presented for the dominant model were included in the qualitative analysis. The use of a dominant model represents the assumption that it is enough for the appearance of one alternative allele to reveal a feature.

Qualitative analysis

All publications not indexed in the PharmGKB database were qualified for the qualitative analysis. The list of variants with the ORs and p-values for the corrected data was included in Table 4.

Three publications describing four variants with a statistically significant correlation with anaemia were found. Lambrechts et al. proved that the presence of rs363717 (*ABCA1*) and rs12762549 (*ABCC2*) was associated with a decreased chance of grade III and IV anaemia. The rs11615 (*ERCC1*) was associated with an increased chance of grade III and IV anaemia. Liblab et al. and Ferracini et al. both described the rs1695 variant located in the *GSTP1* gene. According to Liblab et al., AG genotype was associated with an increased chance of developing grade II anaemia on the CTCAE 4.03 scale. In Ferracini et al., the presence of this variant in the dominant model (AG + GG) was associated with a decrease in the chance of grade III-IV anaemia on the CTCAE 5.0 scale.

One publication describing one variant with a statistically significant correlation with thrombocytopenia was found. In Ferracini et al., rs1695 was associated with a lower chance of grade I-IV thrombocytopenia in the dominant model (AG + GG) compared to the AA reference homozygotes.

Discussion

Completeness and systematic character of the PharmGKB

The study population in the two PharmGKB-indexed publications comes from a phase III randomised clinical trial - The Scottish Randomized Trial in Ovarian Cancer (SCOTROC1). The SCOTROC1 study, compared to the other studies in the systematic review, was characterised by a large study group (808 patients). Additionally, one of the publications that discussed the results of this study (He et al.) was published in Pharmacogenomics Journal. The PharmGKB authors indicate that the results published in journals related to pharmacogenomics are

Table 4. Summary of the effect of statistically significant variants on toxicity.

Author	Variant, gene	Nucleotide change	Assessed genotype or allele	Comparator: genotype or allele	Outcome	OR, 95% CI	p-value
Lambrechts et al.	rs363717, ABCA1	C>T*/**	Genotype TT*/**	Allele C*/**	Anaemia, grade III-IV	0.48 (0.31–0.76)**	0.002
	rs12762549, ABCC2	C>G	Allele G	Genotype CC	Anaemia, grade III-IV	0.51 (0.33–0.81)	0.004
	rs11615, ERCC1	A>G*	Allele G*	Genotype AA*	Anaemia, grade III-IV	1.61 (1.04–2.50)	0.031
Liblab et al.	rs1695, GSTP1	A>G	Genotype AG	Genotype AA	Anaemia, grade II	5.20 (1.00–27.15)	0.036
Ferracini et al.	rs1695, GSTP1	A>G	Genotype AG + GG	Genotype AA	Anaemia, grade III-IV	0.17 (0.04–0.69)	0.010
	rs1695, GSTP1	A>G	Genotype AG + GG	Genotype AA	Thrombocytopenia, grade I-IV	0.27 (0.12–0.64)	<0.01

* Variant description was mapped on the plus strand; ** In data analysis, the OR and the confidence intervals were reversed.

indexed in the database. PharmGKB does not provide information on the date of indexing the records. For this reason, insufficient data were available to assess whether the McWhinney-Glass et al. study, published three years earlier, was indexed due to reference by He et al. to the methodological assumptions implemented in McWhinney-Glass et al. study. Such conclusions could be drawn when the publication would be indexed after the publication of He et al. was recorded in the database. The second reason may have been that the McWhinney-Glass et al. study was published in a high impact factor journal (Clinical Cancer Research, impact factor 10.107 in 2019).

In summary, the reasons for the non-indexing of the remaining three publications included in the review - Lambrechts et al., Liblab et al., Ferracini et al. could have been: 1) publication of articles in journals not related to the subject of pharmacogenetics, 2) a study with fewer patients, 3) a lower impact factor for journals where the articles were published, which made PharmGKB curators less likely to be able to index the study.

Results of included publications

Three publications not indexed in PharmGKB were identified. These studies described six variables relating to the correlation of the variants with the chance of ADRs during platinum compounds treatment. Four variants were associated with a reduction of the chance of ADRs, and two variants were correlated with an increased risk of ADRs occurrence. A correlation between variants and a reduced chance of III-IV grade anaemia was found in rs1695 (*GSTP*), rs363717 (*ABCA*) and rs12762549 (*ABCC2*). In the case of the rs1695 (*GSTP1*) variant, a reduced chance of developing I-IV grade thrombocytopenia was proved.

The variants associated with an increased risk of ADRs were rs11615 (*ERCC1*) in the publication by Lambrechts et al. (III-IV grade anaemia) and rs1695 (*GSTP1*) in Liblab et al. (grade II anaemia). No GG genotype was reported for rs1695 (*GSTP1*) in Liblab et al., making it impossible to test different statistical models; Investigators also did not report any adverse event for anaemia higher than grade II. Notably, only in grade III anaemia, the use of blood transfusion in counteracting ADR is considered, which indicates a significantly higher significance of the impact of this clinical condition on the patient's general condition during treatment with platinum compounds.[28]

The authors in Liblab et al. study proved that the AG genotype in comparison to AA genotype is associated with a higher chance of ADR (OR = 5.20, 95% CI: 1.00–27.15), while in the study by Ferracini et al., the opposite result was described for the AG versus AA genotype (OR = 0.16, 95% CI: 0.03–0.84). However, both publications defined the endpoint differently - in the Liblab et al., grade II anaemia was assessed, and in contrast, in Ferracini et al., the endpoint was more severe anaemia (grade III-IV). The difference in defining the endpoint required a separate analysis of the ORs described by both publications.

Potential biases in the review process

Due to the need to meet the formal requirements related to the master thesis, the process of searching, selection, extraction and data analysis of the results was carried out by one researcher.

The scope of the review included only patients with ovarian cancer, which limited the possibility of collecting additional records beyond those contained in PharmGKB that indexes information on the effects of platinum compounds in other indications.

The review was also limited to treatment with platinum compounds in monotherapy or with paclitaxel or docetaxel. Limiting the scope only to the combination of cisplatin, carboplatin and oxaliplatin with a taxane may have lowered the number of publications that could describe variants involved in the metabolism of platinum compounds and ADR during treatment.

Conclusions

Three new publications describing four statistically significant variants, not indexed in the PharmGKB, were identified. A systematic review should be carried out when looking for information on pharmacogenetic data. Until a fully functional automated indexing process is implemented in the PharmGKB, researchers should consider supplementing data from non-pharmacogenetic journals, smaller sample studies, and lower impact factor journals. According to the information currently published on the PharmGKB website, the database only indexes publications in PubMed, which means that data acquisition is not based on the methodology of a systematic review.

Authors disclose no conflict of interest.

Supplement

Table 5. PubMed search strategy.

No.	Query
1	cancer OR cancers OR cancer* OR oncology OR oncolog* OR neoplasm OR neoplasms OR neoplasm* OR carcinoma OR carcinom* OR tumor OR tumour OR tumor* OR tumour* OR tumors OR tumours OR malignan* OR malignant
2	ovary OR ovarian OR ovaries OR ovarium
3	#1 AND #2
4	pharmacogenetic* OR mutation {tiab} OR mutations {tiab} OR genetic* {tiab} OR variant OR variants OR genomic*
5	'yap1' OR 'xylt2' OR 'xrcc4' OR 'xrcc3' OR 'xrcc1' OR 'xpc' OR 'xpa' OR 'xbp1' OR 'wwox' OR 'wrn' OR 'wnt5b' OR 'wif1' OR 'vegfa' OR 'ugt1a9' OR 'ugt1a7*3' OR 'ugt1a7' OR 'ugt1a6*2a' OR 'ugt1a6' OR 'ugt1a1*60' OR 'ugt1a1*6' OR 'ugt1a1*28' OR 'ugt1a1*1' OR 'ugt1a1' OR 'ube2i' OR 'tyms' OR 'tymp' OR 'trim5' OR 'tpmt*3c' OR 'tpmt*3b' OR 'tpmt*3a' OR 'tpmt*2' OR 'tpmt*1' OR 'tpmt' OR 'tp53' OR 'tnf' OR 'tigd1' OR 'tac1' OR 'syne3' OR 'sox10' OR 'sod3' OR 'sod2' OR 'smad7' OR 'slco1b3' OR 'slc47a1' OR 'slc31a1' OR 'slc22a2' OR 'slc22a1' OR 'slc19a1' OR 'slc16a5' OR 'serpinc1' OR 'serpina5' OR 'sele' OR 'scn10a' OR 'rs9981861' OR 'rs9937' OR 'rs9825762' OR 'rs9679162' OR 'rs9597' OR 'rs9535828' OR 'rs9535826' OR 'rs939338' OR 'rs9369421' OR 'rs9332377' OR 'rs9262143' OR 'rs9262132' OR 'rs886424' OR 'rs886423' OR 'rs885036' OR 'rs879825' OR 'rs879207' OR 'rs873601' OR 'rs863221' OR 'rs861539' OR 'rs854560' OR 'rs843748' OR 'rs833061' OR 'rs830884' OR 'rs8187710' OR 'rs8020368' OR 'rs7999812' OR 'rs7993418' OR 'rs797519' OR 'rs7958904' OR 'rs7952081' OR 'rs7950311' OR 'rs79419059' OR 'rs7940013' OR 'rs7937567' OR 'rs7921977' OR 'rs7851395' OR 'rs780094' OR 'rs780093' OR 'rs773123' OR 'rs7686909' OR 'rs7667298' OR 'rs7664413' OR 'rs763110' OR 'rs7608731' OR 'rs751402' OR 'rs75017182' OR 'rs7483' OR 'rs74090038' OR 'rs7402844' OR 'rs73594404' OR 'rs73450548' OR 'rs7325568' OR 'rs7311358' OR 'rs726501' OR 'rs725518' OR 'rs720106' OR 'rs7186128' OR 'rs7180135' OR 'rs717620' OR 'rs7170924' OR 'rs7170769' OR 'rs716274' OR 'rs715171' OR 'rs7131224' OR 'rs7121' OR 'rs7091672' OR 'rs7014346' OR 'rs7013278' OR 'rs699947' OR 'rs6983267' OR 'rs698' OR 'rs6900017' OR 'rs6877011' OR 'rs6848982' OR 'rs683369' OR 'rs6832850' OR 'rs6769511' OR 'rs6752303' OR 'rs67376798' OR 'rs6721961' OR 'rs664393' OR 'rs662' OR 'rs6504649' OR 'rs6498486' OR 'rs6458232' OR 'rs6413432' OR 'rs62107593' OR 'rs619586' OR 'rs61764370' OR 'rs6151031' OR 'rs6119' OR 'rs6118' OR 'rs6113' OR 'rs60369023' OR 'rs6025211' OR 'rs5934731' OR 'rs5925720' OR 'rs5906072' OR 'rs5883064' OR 'rs5877' OR 'rs56038477' OR 'rs560018' OR 'rs544093' OR 'rs5275' OR 'rs50872' OR 'rs5009910' OR 'rs4979223' OR 'rs4978536' OR 'rs4939827' OR 'rs4936453' OR 'rs4932551' OR 'rs4880' OR 'rs4834232' OR 'rs4788863' OR 'rs4779584' OR 'rs4759314' OR 'rs4752269' OR 'rs4752220' OR 'rs4752219' OR 'rs465646' OR 'rs4655567' OR 'rs4646437' OR 'rs4646316' OR 'rs4638843' OR 'rs462779' OR 'rs45445694' OR 'rs4541111' OR 'rs451774' OR 'rs4492666' OR 'rs4462560' OR 'rs4426527' OR 'rs4413407' OR 'rs4402960' OR 'rs4377367' OR 'rs4353229' OR 'rs430397' OR 'rs4246215' OR 'rs4244809' OR 'rs4243761' OR 'rs4149117' OR 'rs4148737' OR 'rs4148416' OR 'rs4148323' OR 'rs4124874' OR 'rs3957357' OR 'rs3918290' OR 'rs3917412' OR 'rs3842761' OR 'rs3832043' OR 'rs3817657' OR 'rs3810366' OR 'rs3807598' OR 'rs3803304' OR 'rs3787554' OR 'rs3743773' OR 'rs3740556' OR 'rs3740066' OR 'rs3738948' OR 'rs36120609' OR 'rs36080650' OR 'rs3594' OR 'rs34716810' OR 'rs34116584' OR 'rs3219484' OR 'rs3213239' OR 'rs3212986' OR 'rs3212948' OR 'rs3204953' OR 'rs316019' OR 'rs316003' OR 'rs3136228' OR 'rs3130985' OR 'rs3130907' OR 'rs3130' OR 'rs3115672' OR 'rs3114018' OR 'rs3094086' OR 'rs3087403' OR 'rs3087399' OR 'rs3087386' OR 'rs307822' OR 'rs307805' OR 'rs3025039' OR 'rs2978931' OR 'rs2978926' OR 'rs293795' OR 'rs2936519' OR 'rs2928609' OR 'rs2928608' OR 'rs2928607' OR 'rs2912024' OR 'rs2900420' OR 'rs2849380' OR 'rs2839698' OR 'rs28362731' OR 'rs2804402' OR 'rs2762939' OR 'rs2740574' OR 'rs2725335' OR 'rs2720376' OR 'rs2699887' OR 'rs26279' OR 'rs2612091' OR 'rs25648' OR 'rs2549714' OR 'rs25489' OR 'rs25487' OR 'rs2498804' OR 'rs2498786' OR 'rs2494752' OR 'rs2494750' OR 'rs244898' OR 'rs238406' OR 'rs2338' OR 'rs232043' OR 'rs2305948' OR 'rs2299939' OR 'rs2298881' OR 'rs2296147' OR 'rs2291767' OR 'rs2289669' OR 'rs2286455' OR 'rs2284922' OR 'rs2284449' OR 'rs2279744' OR 'rs2276466' OR 'rs2276464' OR 'rs2275112' OR 'rs2273697' OR 'rs2269577' OR 'rs2266637' OR 'rs2249825' OR 'rs2236225' OR 'rs2234767' OR 'rs2233980' OR 'rs2233914' OR 'rs2233678' OR 'rs2231142' OR 'rs2230641' OR 'rs2229571' OR 'rs2229046' OR 'rs2228171' OR 'rs2228100' OR 'rs2228001' OR 'rs2228000' OR 'rs2227310' OR 'rs2207396' OR 'rs2166219' OR 'rs2107425' OR 'rs2094258' OR 'rs2075685' OR 'rs2075252' OR 'rs2074087' OR 'rs2073016' OR 'rs2072671' OR 'rs2071559' OR 'rs2071554' OR 'rs2070676' OR 'rs2070096' OR 'rs2038067' OR 'rs2032582' OR 'rs2031920' OR 'rs2027701' OR 'rs2018683' OR 'rs2010963' OR 'rs1899663' OR 'rs1885301' OR 'rs1872328' OR 'rs1870377' OR 'rs1870134' OR 'rs1863332' OR 'rs1859168' OR 'rs183484' OR 'rs1829346' OR 'rs1805087' OR 'rs1801368' OR 'rs1801320' OR 'rs1801280' OR 'rs1801265' OR 'rs1801249' OR 'rs1801159' OR 'rs1801158' OR 'rs1801133' OR 'rs1801131' OR 'rs1800975' OR 'rs1800734' OR 'rs1800629' OR 'rs1800566' OR 'rs1800460' OR 'rs1800440' OR 'rs1799983' OR 'rs1799895' OR 'rs1799801' OR 'rs1799794' OR 'rs1799793' OR 'rs1799782' OR 'rs1799735' OR 'rs17661089' OR 'rs17655' OR 'rs17626122' OR 'rs17574269' OR 'rs174538' OR 'rs17435' OR 'rs17376848' OR 'rs1734791' OR 'rs1734787' OR 'rs17309872' OR 'rs17216177' OR 'rs17140129' OR 'rs16950650' OR 'rs1695' OR 'rs16944' OR 'rs1690924' OR 'rs16886403' OR 'rs1656402' OR 'rs1649942' OR 'rs163182' OR 'rs1617640' OR 'rs1523130' OR 'rs1523127' OR 'rs1478486' OR 'rs1470383' OR 'rs1453542' OR 'rs1412125' OR 'rs1409314' OR 'rs139887' OR 'rs1346044' OR 'rs13338697' OR 'rs1333049' OR 'rs13181' OR 'rs12999804' OR 'rs12819505' OR 'rs12806698' OR 'rs12659' OR 'rs12621220' OR 'rs12613732' OR 'rs12415607' OR 'rs12201199' OR 'rs121434568' OR 'rs12139042' OR 'rs12118636' OR 'rs1209950' OR 'rs12090346' OR 'rs12023000' OR 'rs11997869' OR 'rs11868547' OR 'rs11710163' OR 'rs116907618' OR 'rs11646213' OR 'rs11623866' OR 'rs11615' OR 'rs11572078' OR 'rs11479' OR 'rs1143623' OR 'rs1142345' OR 'rs1138272' OR 'rs1136201' OR 'rs1131341' OR 'rs1130409' OR 'rs1130214' OR 'rs1128503' OR 'rs11280056' OR 'rs1127687' OR 'rs112445441' OR 'rs11229' OR 'rs11226' OR 'rs11211524' OR 'rs11198804' OR 'rs11030918' OR 'rs10981694' OR 'rs10964552' OR 'rs10950831' OR 'rs10929302' OR 'rs10895256' OR 'rs10886342' OR 'rs10885' OR 'rs10878232' OR 'rs10817465' OR 'rs10817464' OR 'rs10795668' OR 'rs10787899' OR 'rs10759637' OR 'rs1065634' OR 'rs1061472' OR 'rs1059698' OR 'rs1058932' OR 'rs1056836' OR 'rs1052555' OR 'rs1052536' OR 'rs1052133' OR 'rs1051740' OR 'rs10517' OR 'rs1051640' OR 'rs10513202' OR 'rs1051266' OR 'rs10510050' OR 'rs1050565' OR 'rs1049709' OR 'rs1049305' OR 'rs10491684' OR 'rs10486003' OR 'rs1047768' OR 'rs1045642' OR 'rs1045411' OR 'rs1044457' OR 'rs10434' OR 'rs1042927' OR 'rs1042858' OR 'rs1042522' OR 'rs10276036' OR 'rs10209881' OR 'rs10132552' OR 'rs10120688' OR 'rs10040363' OR 'rrm1' OR 'rnf8' OR 'rev3l' OR 'rev1' OR 'rars' OR 'raf1' OR 'rad52' OR 'rad51' OR 'ptgs2' OR 'pten' OR 'prrc2a' OR 'prom1' OR 'ppp1r18' OR 'ppard' OR 'pon1' OR 'pin1' OR 'pik3ca' OR 'pard3b' OR 'otos' OR 'or4d6' OR 'oprm1' OR 'ogg1' OR 'nup107' OR 'nrg3' OR 'nras' OR 'nr1i2' OR 'nqo1' OR 'nos3' OR 'nfe2l2' OR 'neil1' OR 'nat2' OR 'mutyh' OR 'mucl3' OR 'mtr' OR 'mtor' OR 'mthfr' OR 'mthfd1' OR 'msh6' OR 'msh5' OR 'msh3' OR 'msh2' OR 'mllt3' OR 'mlh1' OR 'mgat4a' OR 'meg3' OR 'mecp2' OR 'mdm2' OR 'map3k1' OR 'malat1' OR 'mad1l1' OR 'lrp2' OR 'lig3' OR 'larp1b' OR 'kras' OR 'klc3' OR 'kdr' OR 'kcnq1' OR 'itga1' OR 'ins-igf2' OR 'il1b' OR 'il16' OR 'igf2bp2' OR 'igf2-as' OR 'igf2' OR 'hspa5' OR 'hottip' OR 'hotair' OR 'hmgb2' OR 'hmgb1' OR 'hla-dob' OR 'hla-c' OR 'hcp5' OR 'h19' OR 'gstt1 null' OR 'gstt1 non-null' OR 'gstt1' OR 'gstp1' OR 'gstm4' OR 'gstm3' OR 'gstm1 null' OR 'gstm1 non-null' OR 'gstm1' OR 'gsta1' OR 'gsr' OR 'gpx5' OR 'gnas' OR 'gckr' OR 'galnt18' OR 'galnt14' OR 'foxc1' OR 'fntb' OR 'flt4' OR 'flt1' OR 'fen1' OR 'faslg' OR 'fas' OR 'fars2' OR 'ets2' OR 'esr1' OR 'ercc5' OR 'ercc4' OR 'ercc3' OR 'ercc2' OR 'ercc1' OR 'erbb3' OR 'erbb2' OR 'epo' OR 'ephx1' OR 'enosf1' OR 'eif4e2' OR 'eif3a' OR 'egfr' OR 'dync2h1' OR 'dux1' OR 'dscam' OR 'dpyd' OR 'dock8' OR 'dleu7' OR 'ddx53' OR 'dcbld1' OR 'cyp3a5*3' OR 'cyp3a5*1' OR 'cyp3a5' OR 'cyp3a4*3' OR 'cyp3a4*22' OR 'cyp3a4*1b' OR 'cyp3a4*1' OR 'cyp3a4' OR 'cyp3a' OR 'cyp2e1' OR 'cyp2c8*3' OR 'cyp2c8' OR 'cyp2a6*9' OR 'cyp2a6*7' OR 'cyp2a6*4a' OR 'cyp2a6*4' OR 'cyp2a6*1a' OR 'cyp2a6' OR 'cyp24a1' OR 'cyp1b1' OR 'cxxc4' OR 'comt' OR 'cmpk1' OR 'cdsn' OR 'cdkn2b-as1' OR 'cdh13' OR 'cda' OR 'ccnh' OR 'casp7' OR 'casp3' OR 'camk2n1' OR 'c6orf15' OR 'c18orf56' OR 'btg4' OR 'blmh' OR 'bcl2' OR 'bard1' OR 'axin2' OR 'atp7b' OR 'atat1' OR 'arhgef4' OR 'aqp1' OR 'apobec2' OR 'aplf' OR 'apex1' OR 'aldh3a1' OR 'aldh1a1' OR 'akt2' OR 'akt1' OR 'agxt' OR 'adh1c' OR 'acyp2a6*7' OR 'acyp2' OR 'acss2' OR 'abcg2' OR 'abcc5' OR 'abcc4' OR 'abcc3' OR 'abcc2' OR 'abcc1' OR 'abcb5' OR 'abcb1'
6	#4 OR #5
7	#3 AND #6
8	carboplatin {tiab} OR platin* {tiab} OR cisplatin {tiab} OR oxaliplatin {tiab}
9	#7 AND #8
10	toxicity OR "side effect" OR "side effects" OR ADR OR "adverse drug reaction" OR "adverse drug reactions" OR ADE OR "adverse drug event" OR "adverse drug events" OR metabolism {tiab}
11	#9 AND #10
12	#11 AND (2010:2020{pdat})

Table 6. Embase search strategy.

	Query
1	'cancer'/exp OR cancer OR 'cancers'/exp OR cancers OR cancer* OR 'oncology'/exp OR oncology OR oncolog* OR 'neoplasm'/exp OR neoplasm OR 'neoplasms'/exp OR neoplasms OR neoplasm* OR 'carcinoma'/exp OR carcinoma OR carcinom* OR 'tumor'/exp OR tumor OR 'tumour'/exp OR tumour OR tumor* OR tumour* OR 'tumors'/exp OR tumors OR tumours OR malignan* OR malignant
2	'ovary'/exp OR ovary OR ovarian OR 'ovaries'/exp OR ovaries OR 'ovarium'/exp OR ovarium
3	#1 AND #2
4	pharmacogenetic* OR mutation:ti,ab OR mutations:ti,ab OR genetic*:ti,ab OR 'variant' OR 'variant'/exp OR variant OR variants OR genomic*
5	'yap1' OR 'xylt2' OR 'xrcc4' OR 'xrcc3' OR 'xrcc1' OR 'xpc' OR 'xpa' OR 'xbp1' OR 'wwox' OR 'wrn' OR 'wnt5b' OR 'wif1' OR 'vegfa' OR 'ugt1a9' OR 'ugt1a7*3' OR 'ugt1a7' OR 'ugt1a6*2a' OR 'ugt1a6' OR 'ugt1a1*60' OR 'ugt1a1*6' OR 'ugt1a1*28' OR 'ugt1a1*1' OR 'ugt1a1' OR 'ube2i' OR 'tyms' OR 'tymp' OR 'trim5' OR 'tpmt*3c' OR 'tpmt*3b' OR 'tpmt*3a' OR 'tpmt*2' OR 'tpmt*1' OR 'tpmt' OR 'tp53' OR 'tnf' OR 'tigd1' OR 'tac1' OR 'syne3' OR 'sox10' OR 'sod3' OR 'sod2' OR 'smad7' OR 'slco1b3' OR 'slc47a1' OR 'slc31a1' OR 'slc22a2' OR 'slc22a1' OR 'slc19a1' OR 'slc16a5' OR 'serpinc1' OR 'serpina5' OR 'sele' OR 'scn10a' OR 'rs9981861' OR 'rs9937' OR 'rs9825762' OR 'rs9679162' OR 'rs9597' OR 'rs9535828' OR 'rs9535826' OR 'rs939338' OR 'rs9369421' OR 'rs9332377' OR 'rs9262143' OR 'rs9262132' OR 'rs886424' OR 'rs886423' OR 'rs885036' OR 'rs879825' OR 'rs879207' OR 'rs873601' OR 'rs863221' OR 'rs861539' OR 'rs854560' OR 'rs843748' OR 'rs833061' OR 'rs830884' OR 'rs8187710' OR 'rs8020368' OR 'rs7999812' OR 'rs7993418' OR 'rs797519' OR 'rs7958904' OR 'rs7952081' OR 'rs7950311' OR 'rs79419059' OR 'rs7940013' OR 'rs7937567' OR 'rs7921977' OR 'rs7851395' OR 'rs780094' OR 'rs780093' OR 'rs773123' OR 'rs7686909' OR 'rs7667298' OR 'rs7664413' OR 'rs763110' OR 'rs7608731' OR 'rs751402' OR 'rs75017182' OR 'rs7483' OR 'rs74090038' OR 'rs7402844' OR 'rs73594404' OR 'rs73450548' OR 'rs7325568' OR 'rs7311358' OR 'rs726501' OR 'rs725518' OR 'rs720106' OR 'rs7186128' OR 'rs7180135' OR 'rs717620' OR 'rs7170924' OR 'rs7170769' OR 'rs716274' OR 'rs715171' OR 'rs7131224' OR 'rs7121' OR 'rs7091672' OR 'rs7014346' OR 'rs7013278' OR 'rs699947' OR 'rs6983267' OR 'rs698' OR 'rs6900017' OR 'rs6877011' OR 'rs6848982' OR 'rs683369' OR 'rs6832850' OR 'rs6769511' OR 'rs6752303' OR 'rs67376798' OR 'rs6721961' OR 'rs664393' OR 'rs662' OR 'rs6504649' OR 'rs6498486' OR 'rs6458232' OR 'rs6413432' OR 'rs62107593' OR 'rs619586' OR 'rs61764370' OR 'rs6151031' OR 'rs6119' OR 'rs6118' OR 'rs6113' OR 'rs60369023' OR 'rs6025211' OR 'rs5934731' OR 'rs5925720' OR 'rs5906072' OR 'rs5883064' OR 'rs5877' OR 'rs56038477' OR 'rs560018' OR 'rs544093' OR 'rs5275' OR 'rs50872' OR 'rs5009910' OR 'rs4979223' OR 'rs4978536' OR 'rs4939827' OR 'rs4936453' OR 'rs4932551' OR 'rs4880' OR 'rs4834232' OR 'rs4788863' OR 'rs4779584' OR 'rs4759314' OR 'rs4752269' OR 'rs4752220' OR 'rs4752219' OR 'rs465646' OR 'rs4655567' OR 'rs4646437' OR 'rs4646316' OR 'rs4638843' OR 'rs462779' OR 'rs45445694' OR 'rs4541111' OR 'rs451774' OR 'rs4492666' OR 'rs4462560' OR 'rs4426527' OR 'rs4413407' OR 'rs4402960' OR 'rs4377367' OR 'rs4353229' OR 'rs430397' OR 'rs4246215' OR 'rs4244809' OR 'rs4243761' OR 'rs4149117' OR 'rs4148737' OR 'rs4148416' OR 'rs4148323' OR 'rs4124874' OR 'rs3957357' OR 'rs3918290' OR 'rs3917412' OR 'rs3842761' OR 'rs3832043' OR 'rs3817657' OR 'rs3810366' OR 'rs3807598' OR 'rs3803304' OR 'rs3787554' OR 'rs3743773' OR 'rs3740556' OR 'rs3740066' OR 'rs3738948' OR 'rs36120609' OR 'rs36080650' OR 'rs3594' OR 'rs34716810' OR 'rs34116584' OR 'rs3219484' OR 'rs3213239' OR 'rs3212986' OR 'rs3212948' OR 'rs3204953' OR 'rs316019' OR 'rs316003' OR 'rs3136228' OR 'rs3130985' OR 'rs3130907' OR 'rs3130' OR 'rs3115672' OR 'rs3114018' OR 'rs3094086' OR 'rs3087403' OR 'rs3087399' OR 'rs3087386' OR 'rs307822' OR 'rs307805' OR 'rs3025039' OR 'rs2978931' OR 'rs2978926' OR 'rs293795' OR 'rs2936519' OR 'rs2928609' OR 'rs2928608' OR 'rs2928607' OR 'rs2912024' OR 'rs2900420' OR 'rs2849380' OR 'rs2839698' OR 'rs28362731' OR 'rs2804402' OR 'rs2762939' OR 'rs2740574' OR 'rs2725335' OR 'rs2720376' OR 'rs2699887' OR 'rs26279' OR 'rs2612091' OR 'rs25648' OR 'rs2549714' OR 'rs25489' OR 'rs25487' OR 'rs2498804' OR 'rs2498786' OR 'rs2494752' OR 'rs2494750' OR 'rs244898' OR 'rs238406' OR 'rs2338' OR 'rs232043' OR 'rs2305948' OR 'rs2299939' OR 'rs2298881' OR 'rs2296147' OR 'rs2291767' OR 'rs2289669' OR 'rs2286455' OR 'rs2284922' OR 'rs2284449' OR 'rs2279744' OR 'rs2276466' OR 'rs2276464' OR 'rs2275112' OR 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6	#4 OR #5
7	#3 AND #6
8	carboplatin:ti,ab OR platin*:ti,ab OR cisplatin:ti,ab OR 'oxaliplatin':ti,ab
9	#7 AND #8
10	'toxicity' OR 'toxicity'/exp OR toxicity OR 'side effect'/exp OR 'side effect' OR 'side effects' OR adr OR 'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse drug reactions' OR ade OR 'adverse drug event'/exp OR 'adverse drug event' OR 'adverse drug events' OR metabolism:ti,ab
11	#9 AND #10
12	#11 AND {2010-2021}/py

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