

Patient	XXX, XX
ID #	Female (*DD.MM.YYYY)
Sample receipt	XXX
Material	Saliva
Report date	XXX
Report-ID	R#

Genetic Report – XXX, XX (*DD.MM.YYYY)

Order Prevention-Panel (Module 01 - Module 09 and Module 12 - Module 14)

Results Overview

Tumor diseases (Module 01)

- Cardiovascular diseases (Module 02)
- Thrombosis and coagulation disorders (Module 03)
- Iron and copper storage diseases (Module 04)
- Hypercholesterolemia (Module 05)
- Eye diseases (Module 06)
- Malignant hyperthermia (Module 07)

Pharmacogenetics (Module 08)

- Familial diabetes (Module 09)
- Adult-onset inborn errors of metabolism (Module 12)
- Kidney diseases (Module 13)
- Actionable Core Gene Set According to ACMG (Module 14)

Variant found in gene *ATM*

- Without pathological findings
- Without pathological findings
- Without pathological findings
- Without pathological findings
- Without pathological findings
- Without pathological findings

Individual recommendations (see separate report)

- Without pathological findings
- Without pathological findings
- Without pathological findings
- Without pathological findings

Within the genes listed in module 01-07, 09 and 12-14, we did not detect any further pathogenic variants, aside from those listed below, which are associated with an increased disease risk.

Results

- **Detection of a pathogenic variant in gene *ATM*, which is associated with an increased cancer risk.**

Gene	Variant	Zygoty	Heredity	MAF (%)	Classification
<i>ATM</i>	c.4683_4689del; p.Asp1563Phefs*36 chr11:108164109-108164116 CTTTGA>C (hg19)	het.	AD, AR	< 0.01	pathogenic

Information for the interpretation of this table can be found in section *Additional Information*.

Recommendation

We advise that the individuals requesting genetic services should discuss, in detail, the consequences of the results for themselves and family members with an approved genetic counsellor.

Genetic Relevance

Your proband is heterozygous for a pathogenic variant in gene *ATM*. This may be of relevance for at-risk family members.

Individual variants have a 50% probability of being passed on to each respective offspring.

Clinical Information and Variant Interpretation

ATM, NM_000051.4

OMIM / Reference	Phenotype	Heredity
208900	Ataxia-telangiectasia (AT)	AR
114480	Breast cancer, susceptibility to	AD

The *ATM* gene encodes a member of the phosphatidylinositol 3-kinase family of proteins that responds to DNA damage by phosphorylating key substrates involved in DNA repair and / or cell cycle control. Biallelic pathogenic variants in the *ATM* gene, which lead to chromosomal instability (Iourov et al., 2009, PMID: 19414482), can cause the recessive disorder ataxia-telangiectasia (AT), which begins in early childhood and is characterized by cerebellar ataxia, telangiectasias, immune defects, and an increased risk for cancer. Non-classical forms of AT include a less progressive course of the disease, adult onset, and often the development of dystonia (Veenhuis, updated 10/2023, PMID: 20301790, GeneReviews). The cancer risk of individuals heterozygous for a pathogenic variant in the *ATM* gene has been reported to be moderately elevated, primarily because of the increased risk for breast cancer (Rosenthal et al., 2017, PMID: 28011157; Jerzak et al., 2018, PMID: 29719442; Moslemi et al., 2021, PMID: 33402103). A large-scale study also demonstrated a moderately to severely increased risk of pancreatic, prostate, and gastric cancers, among others. Slightly to moderately increased risk was shown for ovarian cancer, male breast cancer, colorectal cancer, and melanoma, among others (Hall et al., 2021, PMID: 33509806).

ATM, c.4683_4689del; p.Asp1563Phefs*36 (het.), ClinVar ID: 265382

ACMG/ACGS Criterion	Points	Description																				
PVS1	+8	The variant likely results in a loss (or truncation) of the protein, which is a known pathomechanism for ATM-associated disease.																				
PM2	+2	This variant is listed in the gnomAD global population dataset with a very low frequency.																				
ACMG/ACGS Classification: pathogenic	+10	<table border="1"><tr><td>B</td><td>LB</td><td>VUS (Ice Cold)</td><td>VUS (Cold)</td><td>VUS (Cool)</td><td>VUS (Tepid)</td><td>VUS (Warm)</td><td>VUS (Hot)</td><td>LP</td><td>P</td></tr><tr><td>≤ -7</td><td>-6 - -1</td><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6 - 9</td><td>≥ 10</td></tr></table>	B	LB	VUS (Ice Cold)	VUS (Cold)	VUS (Cool)	VUS (Tepid)	VUS (Warm)	VUS (Hot)	LP	P	≤ -7	-6 - -1	0	1	2	3	4	5	6 - 9	≥ 10
B	LB	VUS (Ice Cold)	VUS (Cold)	VUS (Cool)	VUS (Tepid)	VUS (Warm)	VUS (Hot)	LP	P													
≤ -7	-6 - -1	0	1	2	3	4	5	6 - 9	≥ 10													


Genetic counseling should be offered with all diagnostic genetic testing. For predictive tests genetic counseling has to be offered.

Medical report written by: XXX

Proofread by: XXX

Validated by: XXX

With kind regards,


Dr. med. Dr. rer. nat. Saskia Biskup
Board Certified Human Geneticist

Additional Information

Requested Genes Modules 01-09 and 12-14, which have been requested in the context of this investigation, contain the following genes:

Module 01: APC, ATM, AXIN2, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDKN2A, CHEK2, DICER1, EPCAM, FH, FLCN, KIT, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, NF2, PALB2, PDGFRA, PMS2, POLD1, POLE, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, STK11, TMEM127, TP53, TSC1, TSC2, VHL, WT1 (Tumor diseases)

Module 02: ACTA2, ACTC1, ACVRL1, ALPK3, BAG3, BMPR2, CALM1, CALM2, CALM3, CASQ2, CAV1, COL3A1, DES, DSC2, DSG2, DSP, EMD, ENG, FBN1, FHL1, FLNC, GDF2, KCNH2, KCNK3, KCNQ1, KDR, LAMP2, LMNA, LOX, MYBPC3, MYH11, MYH7, MYL2, MYL3, MYLK, PKP2, PLN, PRKAG2, RBM20, RYR2, SCN5A, SMAD3, SMAD9, TBX4, TECRL, TGFB2, TGFB1, TGFB2, TMEM43, TNNC1, TNNI3, TNNI2, TPM1, TRDN, TTN, TTR (Cardiovascular diseases)

Module 03: ADAMTS13, F10, F11, F12, F13A1, F13B, F2, F5, F7, F8 (complex intronic rearrangements not included), F9, GFI1B, GP1BA, GP1BB, GP6, GP9, HRG, ITGA2B, ITGB3, LMAN1, MCFD2, NBEAL2, PROC, PROS1, SERPINC1, SERPIND1, SERPINF2, VWF (Thrombosis and coagulation disorders)

Module 04: ATP7B, CP, GLRX5, HAMP, HFE, HJV, SLC40A1, TFR2 (Iron and copper storage diseases)

Module 05: APOB, LDLR, LDLRAP1, PCSK9 (Hypercholesterolemia)

Module 06: ABCA4, CRB1, GUCY2D, MYOC, RPE65 (Eye diseases)

Module 07: CACNA1S, RYR1 (Malignant hyperthermia)

Module 08: *ABCG2, CACNA1S, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, CYP4F2, DPYD, G6PD, HLA-A, HLA-B, IFNL3, MT-RNR1, NUDT15, RYR1, SLCO1B1, TPMT, UGT1A1, VKORC1* (Pharmacogenetics)

Module 09: *ABCC8, GCK, HNF1A, HNF1B, HNF4A, INS, KCNJ11, PDX1* (Familial diabetes)

Module 12: *ABCD1, ACADVL, ARSA, ATP7B, BTBD, COQ2, CPT2, CYP27A1, DLAT, ETFA, ETFB, ETFDH, GAA, GALC, GBA1, GLA, HGD, IDUA, MMACHC, NPC1, OTC, PAH, PCCA, PCCB, SERPINA1, TH, TPPA* (Adult-onset inborn errors of metabolism)

Module 13: *PKD1, PKD2* (Kidney diseases)

Module 14: *ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BAG3, BMPR1A, BRCA1, BRCA2, BTBD, CACNA1S, CALM1, CALM2, CALM3, CASQ2, COL3A1, DES, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11, MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RBM20, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNC1, TNNT1, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, TTR, VHL, WT1* (Actionable Core Gene Set According to ACMG)

Due to the existence of pseudogenes, variants detected in the homologous regions of the genes *PMS2* (NM_000535.7) and *TTN* (NM_133378.4) cannot be further evaluated, as it is not possible to distinguish these regions.

General Remarks

Additional variants may be present within regions which were not analyzed (e.g. introns, promoter and enhancer regions and long repeats). A lower specificity enrichment and/or inaccurate variant calling cannot be ruled out for homologous regions with multiple genomic copies. The occurrence of low frequency somatic mosaicism cannot be reliably assessed using a pipeline optimized for germline variant detection, and may therefore remain undetected. Moreover, detection of large deletions and duplications is not guaranteed by next-generation high-throughput sequencing. Further the degree of heteroplasmy of mitochondrial variants can vary remarkably between different tissues (Wallace & Chalkia 2013; PMID: 24186072). Therefore, it is possible that disease causing variants, deletions and duplications are not detectable in the mtDNA from leucocytes, but present in other tissues. The classification of variants may change in the future due to new evidence or improvements in scientific understanding.

Information for the interpretation of the tables

Heredity: AD – autosomal dominant, AR – autosomal recessive, XL – X-linked, mito – mitochondrial

MAF: The *minor allele frequency* describes the least frequent allele at a specific locus in a given population. For mitochondrial variants, the population frequency (MAF column) is based on the homoplasmic frequency within a reference population (gnomAD).

Classification: Variant classification is based on ACMG, ACGS-2020v4.01, and ClinGen SVI WG guidelines (Richards et al., 2015, PMID: 25741868; Ellard et al., 2020, Association for Clinical Genomic Science; <https://clinicalgenome.org/working-groups/sequence-variant-interpretation/>). If applicable, the following approach is used. The weighting of criteria and their modification follows the current ACGS guidelines in the strength levels *very strong* (+ 8), *strong* (+/- 4), *moderate* (+/- 2), and *supporting* (+/- 1). According to the respective category (pathogenic or benign) and criterion strength, positive or negative points are assigned as mentioned above (Tavtigian et al., 2020, PMID: 32720330). Variants of uncertain significance (VUS) are subcategorized into *hot*, *warm*, *tepid*, *cool*, *cold*, and *ice cold* VUS according to their likelihood of reaching a pathogenic classification in the future. Posterior probability decreases from 90% to 10% in this order (Ellard et al., 2020, Association for Clinical Genomic Science). If a variant reaches the classification pathogenic, after checking of all benign criteria, not necessarily all other applicable criteria are listed.

The chromosomal positions of variants listed in the report refer to the human reference genome hg19.

Methods

Sequencing: Protein-coding regions, flanking intronic regions and additional disease-relevant non-coding regions of the nuclear encoded genes, as well as the mitochondrial DNA were enriched using in-solution hybridization technology, and were sequenced using the Illumina NovaSeq 6000/NovaSeq X Plus system.

NGS based CNV-Calling: Copy number variations (CNV) were computed on uniquely mapping, non-duplicate, high-quality reads using an internally developed method based on sequencing coverage depth (only applicable for nuclear encoded genes). Briefly, we used reference samples to create a model of the expected coverage that represents wet-lab biases as well as inter-sample variation. *CNV calling* was performed by computing the sample's normalized coverage profile and its deviation from the expected coverage. Genomic regions are called as variant if they deviate significantly from the expected coverage. Copy number variants are named according to current ISCN guidelines. NGS based CNV-Calling will not detect copy number neutral structural variants such as balanced translocations, inversions, uniparental

heterodisomy or low-level mosaicism. Aberrations within the pseudoautosomal region (PAR) cannot be detected with high accuracy. The integration site of duplications cannot be determined by NGS based CNV-Calling.

Please note that next generation sequencing based detection of copy number variations has lower sensitivity/specificity than a direct quantification method, e.g. MLPA. Copy-neutral structural aberrations cannot be detected using this method (e.g. balanced translocations and balanced inversions). The absence of reported CNVs therefore does not ultimately guarantee the absence of CNVs.

Computational Analysis: Illumina bcl2fastq2 was used to demultiplex sequencing reads. Adapter removal was performed with Skewer. The trimmed reads were mapped to the human reference genome (hg19) using the Burrows Wheeler Aligner. Reads mapping to more than one location with identical mapping score were discarded. Read duplicates that likely result from PCR amplification were removed. The remaining high-quality sequences were used to determine sequence variants (single nucleotide changes and small insertions/deletions). The variants were annotated based on several internal as well as external databases.

Additional Analyses: Deletion and duplication analysis of the genes *BRCA1* and *BRCA2* was performed using MLPA (*multiplex ligation-dependent probe amplification*, MRC Holland). Quantification was performed in comparison to reference sample DNA.

If pathogenic alterations are present within a gene which are not the result of copy number changes (e.g. SNVs), these cannot be detected via MLPA unless covered by variant-specific probes, and therefore cannot be ruled out.

MLPA analysis cannot determine the allele configuration of copy number variants. In rare cases, the presence of an unexpected copy number distribution, e.g. a gene duplication on one allele and a deletion on the other allele, may lead to false negative results.

The data for the pharmacogenetics module were evaluated by SONOGEN AG (Zurich). You will receive the details of these findings in a separate report.

Diagnostic data analysis: Variants were classified and reported based on ACMG/ACGS-2020v4.01 guidelines (Richards et al., 2015, PMID: 25741868, Ellard et al., 2020, Association for Clinical Genomic Science).

Only variants (SNVs/Small Indels) in the coding region and the flanking intronic regions (± 8 bp) of the nuclear encoded genes and in the mitochondrial DNA with a minor allele frequency (MAF) $< 1.5\%$ and known disease-causing variants (according to HGMD[®] and MITOMAP) are evaluated. Possible exceptions include risk factors and hypomorphic alleles. Minor allele frequencies are taken from public databases (e.g. gnomAD, MITOMAP) and an in-house database. If an acceptable sequencing-depth per base is not achieved by high-throughput sequencing, our quality guidelines demand local re-sequencing using classical Sanger-technology.

In this case, 97.67% of the targeted regions were covered by a minimum of 30 high-quality sequencing reads per base. The medical report contains only SNVs, small indels and larger deletions/duplications, which are, based upon the available data, evaluated to be clearly pathogenic or likely pathogenic. Single heterozygous variants in genes, which are exclusively associated with recessive diseases, are not reported.

Variants are named according to the HGVS recommendations without any information regarding *cis* or *trans* configuration.

The results do not rule out the possibility of an increased disease risk in the addressed disease modules.

This analysis will detect variants of uncertain significance which are not clearly associated with disease. If your proband has a conspicuous family history, a genetic consultation could be extended to include the evaluation of unclear variants. A reevaluation of the results can be requested at a later time point.

The sample fulfilled our quality criteria upon arrival and during/after each processing step in the laboratory.

The procedure described above was developed and validated by CeGaT GmbH (Laboratory developed test; LDT).

Communication, dissemination and usage of this report for scientific purposes is only permitted in accordance with the German Genetic Diagnostics Legislation.

SONOGEN XP report for Richard Roe - Brief version

First name: Richard **Laboratory patient ID:** 999999
Last name: Roe **Report date:** January 17, 2025
Date of birth: March 1, 1985
Gender: male

Pharmacogenetic profile

Gene	Genotype	Predicted phenotype/haplotype	Effect
CYP2C9	*1/*2	IM (AS 1.5)	intermediate (slower) metabolism
CYP2C19	*1/*17	RM	fast metabolism
CYP3A5	*3/*3	non-expresser (PM)	very slow metabolism
CYP4F2	*1/*3	IM	intermediate (slower) metabolism
HLA-B	*15:02/*35:01	increased risk (*15:02)	high risk of adverse events
IFNL3	rs12979860-TT	unfavorable response	low response rate
SLCO1B1	*1/*5	decreased function	decreased drug efficacy
UGT1A1	*1/*28	IM	intermediate (slower) metabolism
VKORC1	-1639GA	decreased function	increased drug efficacy
ABCG2	421CC	normal function	normal drug efficacy
CACNA1S	WT/WT	normal risk	normal risk of adverse events
CYP2B6	*1/*1	NM	normal metabolism
CYP2D6	*1/*2	NM	normal metabolism
CYP3A4	*1/*1	NM	normal metabolism
DPYD	*1/*1	NM (AS 2.0)	normal metabolism
G6PD	B/B	normal	normal metabolism
HLA-A	*03:01/*24:02	normal risk	normal risk of adverse events
MT-RNR1	WT	normal risk	normal risk of adverse events
NUDT15	*1/*1	NM	normal risk of adverse events
RYR1	WT/WT	normal risk	normal risk of adverse events
TPMT	*1/*1	NM	normal metabolism

For CYP3A5, the majority of the global population - 52% of Africans, 70% of Asians, and 92% of Europeans - lack functional CYP3A5 expression (without enzymatic activity, non-expresser). This phenotype is considered as the standard ("normal").

For HLA-A, the risk allele *31:01 was considered for phenotype classification.

Drug - PGx interactions of treatment - recommendations

	Normal risk	Use with caution	High risk
abacavir HLA-B normal risk (*57:01-negative)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
abrocitinib CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
acenocoumarol VKORC1 decreased function	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
allopurinol HLA-B normal risk (*58:01-negative)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
allopurinol ABCG2 normal function	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
amikacin MT-RNR1 normal risk	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
amitriptyline CYP2D6 NM, CYP2C19 RM		<ul style="list-style-type: none"> High dose (e.g., depression): Consider alternative drug not metabolized by CYP2C19 (e.g., nortriptyline, desipramine). If amitriptyline is warranted, utilize TDM to guide dose adjustment. Low dose (e.g., neuropathic pain): Follow drug label dosing recommendation. 	
aripiprazole CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
atazanavir UGT1A1 IM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
atomoxetine CYP2D6 NM		<ul style="list-style-type: none"> Start with 40 mg/day and increase to 80 mg/day after 3 days. If no clinical response and in the absence of adverse events after 2 weeks, consider increasing dose to 100 mg/day to approach 400 ng/ml peak plasma concentration. 	
atorvastatin SLCO1B1 decreased function			<ul style="list-style-type: none"> Use not more than 40 mg as a starting dose and adjust doses based on disease-specific guidelines. Be alert to symptoms of myopathy, especially with 40 mg atorvastatin. If the patient has additional risk factors for statin-induced myopathy, choose an alternative drug. If dose over 40 mg is needed, consider combination therapy.
azathioprine Normal thiopurine metabolism	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
belinostat UGT1A1 IM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
brexpiprazole CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
brivaracetam CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
capecitabine DPYD NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		

carbamazepine HLA-A normal risk, HLA-B increased risk (*15:02)			<ul style="list-style-type: none"> Choose alternative treatment in carbamazepine naïve patients. If patient has previously used carbamazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of carbamazepine.
carisoprodol CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
carvedilol CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
celecoxib CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
cevimeline CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
citalopram CYP2C19 RM		<ul style="list-style-type: none"> Initiate therapy with recommended starting dose. If patient does not adequately respond, consider titrating to a higher dose or switching to an alternative not predominantly metabolized by CYP2C19. 	
clobazam CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
clomipramine CYP2D6 NM, CYP2C19 RM		<ul style="list-style-type: none"> High dose (e.g., depression): Consider alternative drug not metabolized by CYP2C19 (e.g. nortriptyline, desipramine). If clomipramine is warranted, utilize TDM to guide dose adjustment. Low dose (e.g., neuropathic pain): Follow drug label dosing recommendation. 	
clopidogrel CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
clozapine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
codeine CYP2D6 NM	<ul style="list-style-type: none"> Use label recommended age- or weight-specific dosing. 		
dapsone G6PD normal	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
desflurane Normal risk of MH	<ul style="list-style-type: none"> RYR1 and CACNA1S phenotypes show no contraindication for the use of volatile anesthetics. 		
desipramine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
deutetrabenazine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
dexlansoprazole CYP2C19 RM		<ul style="list-style-type: none"> Initiate standard starting daily dose. Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. Monitor for efficacy. 	
doxepin CYP2D6 NM, CYP2C19 RM		<ul style="list-style-type: none"> High dose (e.g., depression): Consider alternative drug not metabolized by CYP2C19 (e.g., nortriptyline, desipramine). If doxepin is warranted, utilize TDM to guide dose adjustment. Low dose (e.g., neuropathic pain): Follow drug label dosing recommendation. 	

efavirenz CYP2B6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
eliglustat CYP2D6 NM	<ul style="list-style-type: none"> Use the standard dose of 84 mg twice daily. 		
escitalopram CYP2C19 RM		<ul style="list-style-type: none"> Initiate therapy with recommended starting dose. If patient does not adequately respond, consider titrating to a higher dose or switching to an alternative not predominantly metabolized by CYP2C19. 	
fesoterodine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
flecainide CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
flucloxacillin HLA-B normal risk (*57: 01-negative)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
flucytosine DPYD NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
fluorouracil DPYD NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
flurbiprofen CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
fluvastatin CYP2C9 IM, SLCO1B1 decreased function		<ul style="list-style-type: none"> Use not more than 20 mg as a starting dose and adjust doses based on disease-specific guidelines. If dose >20 mg needed for desired efficacy, consider an alternative statin or combination therapy. 	
fluvoxamine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
gentamicin MT-RNR1 normal risk	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
haloperidol CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
ibuprofen CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
iloperidone CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
imipramine CYP2D6 NM, CYP2C19 RM		<ul style="list-style-type: none"> High dose (e.g., depression): Consider alternative drug not metabolized by CYP2C19 (e.g. nortriptyline, desipramine). If imipramine is warranted, utilize TDM to guide dose adjustment. Low dose (e.g., neuropathic pain): Follow drug label dosing recommendation. 	
irinotecan UGT1A1 IM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
isoflurane Normal risk of MH	<ul style="list-style-type: none"> RYR1 and CACNA1S phenotypes show no contraindication for the use of volatile anesthetics. 		

lamotrigine HLA-B increased risk (*15:02)			<ul style="list-style-type: none"> • Avoid lamotrigine if possible. • Carefully weigh the risk of SJS/TEN against the benefits. • Carbamazepine is not an alternative, as the risk of SJS/TEN is higher. Oxcarbazepine and phenytoin have a similar risk of SJS/TEN. If it is not possible to avoid these products, advise the patient to report any rash immediately.
lansoprazole CYP2C19 RM		<ul style="list-style-type: none"> • Initiate standard starting daily dose. • Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. • Monitor for efficacy. 	
lornoxiam CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
lovastatin SLCO1B1 decreased function			<ul style="list-style-type: none"> • Prescribe an alternative statin. • If lovastatin therapy is warranted, limit dose to 20 mg/day.
mavacamten CYP2C19 RM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
meloxicam CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> • Follow drug label dosing recommendations. 		
mercaptopurine Normal thiopurine metabolism	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
metoprolol CYP2D6 NM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
nitrofurantoin G6PD normal	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
nortriptyline CYP2D6 NM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
omeprazole CYP2C19 RM		<ul style="list-style-type: none"> • Initiate standard starting daily dose. • Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. • Monitor for efficacy. 	
ondansetron CYP2D6 NM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
oxcarbazepine HLA-B increased risk (*15:02)			<ul style="list-style-type: none"> • Choose alternative treatment in oxcarbazepine naïve patients. • If patient has previously used oxcarbazepine for longer than 3 months without incidence of cutaneous adverse reactions, cautiously consider use of oxcarbazepine.
oxycodone CYP2D6 NM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
pantoprazole CYP2C19 RM		<ul style="list-style-type: none"> • Initiate standard starting daily dose. • Consider increasing dose by 50-100% for the treatment of H. pylori infection and erosive esophagitis. Daily dose may be given in divided doses. • Monitor for efficacy. 	
paromomycin MT-RNR1 normal risk	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		
paroxetine CYP2D6 NM	<ul style="list-style-type: none"> • Follow drug label dosing recommendation. 		

pazopanib UGT1A1 IM, HLA-B normal risk (*57:01-negative)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
peginterferon alfa-2a IFNL3-unfavorable-response genotype			<ul style="list-style-type: none"> Low response rates in treatment naïve patients. Approximately 60% chance for SVR after 24–48 weeks of treatment. Consider implications before initiating PEG-interferon-alfa and ribavirin - containing regimens.
peginterferon alfa-2b IFNL3-unfavorable-response genotype			<ul style="list-style-type: none"> Low response rates in treatment naïve patients. Approximately 60% chance for SVR after 24–48 weeks of treatment. Consider implications before initiating PEG-interferon-alfa and ribavirin - containing regimens.
perphenazine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
phenprocoumon VKORC1 decreased function	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
phenytoin HLA-B increased risk (*15:02-positive)			<ul style="list-style-type: none"> If patient is phenytoin-naïve, do not use phenytoin. Avoid carbamazepine and oxcarbazepine.
pimozide CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
piroxicam CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendations. 		
pitavastatin SLCO1B1 decreased function			<ul style="list-style-type: none"> Prescribe 2 mg or less as a starting dose and adjust doses based on disease-specific guidelines. If more than 2 mg is needed for desired efficacy, consider an alternative statin or combination therapy. Be aware of possible increased risk for myopathy especially for doses over 1 mg.
pitolisant CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
pravastatin SLCO1B1 decreased function			<ul style="list-style-type: none"> Use desired starting dose and adjust doses based on disease-specific guidelines. Be aware of possible increased risk for myopathy especially with doses over 40 mg per day.
primaquine G6PD normal	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
propafenone CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
quetiapine CYP3A4 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
rasburicase G6PD normal	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
ribavirin IFNL3-unfavorable-response genotype			<ul style="list-style-type: none"> Low response rates in treatment naïve patients. Approximately 30-60% chance for SVR after 24–48 weeks of treatment. Consider implications before initiating PEG-interferon-alfa and ribavirin-containing regimens.
risperidone CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		

rosuvastatin Decreased transport activity		<ul style="list-style-type: none"> Use desired starting dose and adjust doses based on disease-specific and specific population guidelines. Be aware of possible increased risk for myopathy especially for doses over 20 mg. 	
sacituzumab govitecan UGT1A1 IM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
sertraline CYP2B6 NM, CYP2C19 RM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
sevoflurane Normal risk of MH	<ul style="list-style-type: none"> RYR1 and CACNA1S phenotypes show no contraindication for the use of volatile anesthetics. 		
simvastatin SLCO1B1 decreased function			<ul style="list-style-type: none"> Use an alternative statin. If simvastatin is warranted, limit dose to 20 mg/day and be alert to symptoms of myopathy.
siponimod CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
streptomycin MT-RNR1 normal risk	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
succinylcholine Normal risk of MH	<ul style="list-style-type: none"> RYR1 and CACNA1S phenotypes show no contraindication for the use of succinylcholine. 		
tacrolimus CYP3A5 non-expresser	<ul style="list-style-type: none"> Initiate therapy with standard recommended dose. Use TDM to guide dose adjustments. 		
tamoxifen CYP2D6 NM		<ul style="list-style-type: none"> Initiate therapy with recommended standard of care dosing (tamoxifen 20 mg/day). Avoid moderate and strong CYP2D6 inhibitors. 	
tenoxicam CYP2C9 IM (AS 1.5)	<ul style="list-style-type: none"> Follow drug label dosing recommendations. 		
tetrabenazine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
thioguanine Normal thiopurine metabolism	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
thioridazine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
tobramycin MT-RNR1 normal risk	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
tramadol CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
trimipramine CYP2D6 NM, CYP2C19 RM		<ul style="list-style-type: none"> High dose (e.g. depression): Consider alternative drug not metabolized by CYP2C19 (e.g. nortriptyline, desipramine). If trimipramine is warranted, utilize TDM to guide dose adjustment. Low dose (e.g. neuropathic pain): Follow drug label dosing recommendation. 	
tropisetron CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
venlafaxine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		

voriconazole CYP2C19 RM			<ul style="list-style-type: none"> Choose an alternative agent not mainly metabolized by CYP2C19 (e.g. isavuconazole, liposomal amphotericin B, and posaconazole)
vortioxetine CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		
warfarin Intermediate warfarin sensitivity (incl. CYP4F2)		<ul style="list-style-type: none"> Calculate dose with a warfarin dose algorithm (e.g. http://www.warfarindosing.org). 	
zuclopenthixol CYP2D6 NM	<ul style="list-style-type: none"> Follow drug label dosing recommendation. 		

Predictable drug - PGx interactions

Table shows potential interactions of specific drugs with patient's PGx profile. These drugs are related to biomarkers, for which drug label recommendations or dosing guidelines exist, or for which LoE is at least C. For suggested action and detailed information, please indicate drug of interest in patient's treatment and refer to SONOGEN detailed report or consult drug labels or dosing guidelines.

Normal risk		Use with caution	High risk
abacavir (4)	lornoxepam (1)	amitriptyline (2)	atorvastatin (2)
abrocitinib (2)	mavacamten (1)	atomoxetine (2)	carbamazepine (4)
acenocoumarol (1)	meloxicam (2)	citalopram (2)	lamotrigine (1)
allopurinol (3)	mercaptopurine (3)	clomipramine (2)	lovastatin (1)
amikacin (2)	metoprolol (1)	dexlansoprazole (2)	oxcarbazepine (4)
aripiprazole (2)	nitrofurantoin (2)	doxepin (2)	peginterferon alfa-2a (1)
atazanavir (1)	nortriptyline (2)	escitalopram (2)	peginterferon alfa-2b (2)
azathioprine (3)	ondansetron (1)	fluvastatin (1)	phenytoin (2)
belinostat (2)	oxycodone (2)	imipramine (2)	pitavastatin (2)
brexipiprazole (2)	paromomycin	lansoprazole (2)	pravastatin (1)
brivaracetam (2)	paroxetine (1)	omeprazole (2)	ribavirin (1)
capecitabine (3)	pazopanib (2)	pantoprazole (2)	simvastatin (3)
carisoprodol (2)	perphenazine (2)	rosuvastatin (2)	voriconazole (2)
carvedilol (2)	phenprocoumon (1)	tamoxifen (2)	
celecoxib (2)	pimozide (4)	trimipramine (2)	
cevimeline (2)	piroxicam (2)	warfarin (2)	
clobazam (2)	pitolisant (2)		
clopidogrel (2)	primaquine (4)		
clozapine (2)	propafenone (2)		
codeine (2)	quetiapine (1)		
dapsone (2)	rasburicase (4)		
desflurane	risperidone (1)		
desipramine (2)	sacituzumab govitecan (2)		
deutetrabenazine (2)	sertraline (1)		
efavirenz (2)	sevoflurane (2)		
eliglustat (4)	siponimod (4)		
fesoterodine (2)	streptomycin (2)		
flecainide (1)	succinylcholine (2)		
flucloxacillin (2)	tacrolimus (1)		
flucytosine (3)	tenoxicam (1)		
fluorouracil (3)	tetrabenazine (4)		
flurbiprofen (2)	thioguanine (3)		
fluvoxamine (2)	thioridazine (2)		
gentamicin (2)	tobramycin (2)		
haloperidol (1)	tramadol (2)		
ibuprofen (1)	tropisetron (1)		
iloperidone (2)	venlafaxine (2)		
irinotecan (2)	vortioxetine (2)		
isoflurane	zuclopenthixol (1)		

() PGx information included in the drug label are classified by the Pharmacogenomics Knowledgebase (PharmGKB) into the following biomarker relevance categories: (4) required, (3) recommended, (2) actionable, (1) informative

Disclaimer





The present individual treatment optimization proposal and the related information was generated by SONOGEN XP - a clinical decision support and pharmacogenetic expert system. This software is an in vitro medical device and has been developed according to the directive on in vitro diagnostic medical devices (Directive 98/79/EC of the European Parliament and of the Council). The containing information has been collected and reviewed to our best knowledge, however there is no guarantee that it contains the latest scientific findings and that all adverse or important outcomes will be reported in the literature and integrated in the SONOGEN XP software. The responsibility for a correct drug-treatment prescription lies with the treating physician and the user should always apply his independent professional judgement.

Limitation






This pharmacogenetic test will not detect all the known mutations of a gene. Absence of a detectable gene mutation does not rule out the possibility of an altered phenotype due to the presence of an undetected mutation or due to other factors influencing the drug efficacy, such as drug-drug-interactions, comorbidities or lifestyle habits.

Legend

Biomarker Relevance (BR)

	Genetic testing required. The drug label states that a genetic testing should be conducted before using this drug. This requirement may only be for a subset of patients. If the drug label states a test "should be" performed, this is to be interpreted as a requirement.
	Genetic testing recommended. The drug label states that a genetic testing is recommended before using this drug. This recommendation may only be for a subset of patients. If the drug label states a test "should be considered", this is to be interpreted as a recommendation.
	Actionable PGx. The drug label does not discuss testing for gene variants, but does contain information about changes in efficacy, dosage or toxicity (due to such variants). The drug label may mention contraindication of the drug in a subset of patients but does not require or recommend genetic testing.
	Informative PGx. The drug label mentions a gene/protein is involved in the metabolism or pharmacodynamics of the drug but gives no information to suggest that variation in this gene/protein leads to a different response.

Level of Evidence (LoE)

	The variant-drug combination is based on published incomplete case reports, non-significant studies or in vitro, molecular or functional assay evidence only.
	The variant-drug combination is based on published case reports, well documented, and having relevant pharmacokinetic or clinical endpoints.
	The variant-drug combination shows moderate evidence of an association (it is replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small). Or drug label information on PGx relevant genes with potential influence on pharmacokinetics, without information on specific variants.
	The variant-drug combination shows good evidence of an association (it is replicated in more than one cohort with significant p-values, and preferably will have a strong effect size). Or drug label information on specific variants of PGx relevant genes with potential influence on pharmacokinetics. Or the variant-drug combination and recommendation are reflected in peer reviewed articles.
	The variant-drug combination is reflected in a pharmacogenetic guideline (e.g. CPIC, DPWG), or implemented at a pharmacogenomic research network site (e.g. www.warfarindosing.org) or in another major health system. Or FDA box warning. Or drug label recommendation on pharmacogenetic testing or dosing for specific genotype/phenotype.

For further information, please refer to the detailed report.

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