Genetics in the diagnosis and treatment of cardiovascular diseases

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Supplemental Table 1. Cardiovascular Medications, Single Nucleotide Polymorphisms and Drug Response without Guideline Based Recommendations

CV Medication	Associated Gene (SNP ID)	Drug Response [Ref.]
Aspirin [162, 163]	*PEAR1* (rs12041331, and rs 2768759) Other Genes: *P2RY1, MDR1, PLA2G7, HO1, TBXA2R, ALOX12, ALOX5AP and PON1.*	The A-allele of SNP rs12041331 and the C allele of SNP rs2768759 is associated with reduced effectiveness and increased platelet aggregation/activation, but not with cyclooxygenase-1 activity. Other gene polymorphisms under investigation or weak evidence.
DOAC [164-166]	<u>Dabigatran</u> CES1 rs2244613, rs8192935 ABCB1 rs1045642	<u>Response:</u> Decreased peak and trough concentrations (rs8192935 intron: T > C). Decreased trough concentration and risk of bleeding (rs2244613 intron: C > A). Increased peak concentration and increased risk of bleeding complications (rs1045642). Increased peak concentration (rs4148738).
	<u>Rivaroxaban</u> *ABCB* (rs1128503)	Multiple comparisons between wild (TT) and mutant (CC) genotypes at the rs1128503 locus revealed a significant difference of rivaroxaban trough concentrations. There was no significant correlation between ABCB1 gene variation loci rs1045642, rs1128503, rs4148738 and bleeding events.
	<u>Apixaban</u> ABCG2 rs2231142	The candidate gene analyses showed a statistically significant association with a well-known variant in the drug transporter gene ABCG2 (c.421G > T, rs2231142). Patients carrying this variant had a higher exposure to apixaban [area under the curve (AUC), beta = 151 (95% CI 59–243), p = 0.001]. On average, heterozygotes displayed a 5% increase of AUC and homozygotes a 17% increase of AUC, compared with homozygotes for the wild-type allele. Bleeding or thromboembolic events were not significantly associated with ABCG2 rs2231142.
Statin Therapy [167, 168]	<u>Rosuvastatin</u> ABCG2 (rs2231142)	Reduction in transport capacity, carriers of A allele experience 5-7% greater reduction in LDLc when treated with rosuvastatin.
	<u>Dalcetrapib (CETP Inhibitor.)</u>	Genotype AA was associated with a minor reduction in

	ADCY9 (rs1967309)	cardiovascular events whereas genotype GG showed a slight increase in events.
Anti-hypertension medications [169-173]	Verapamil NOS1AP (rs10494366)	rs10494366 GG genotype showed significantly more QTc prolongation than users with the TT genotype [25.4 ms (95% CI: 5.9-44.9)]
	Spironolactone SAGT, CYP11B2	Predictors of response in HFrEF. After 6 months of spironolactone treatment, change in the left ventricular ejection fraction (LVEF) differed by AGT rs699 (CC, 14.6%; TC, 7.9%; TT, 2.7%; P = 2.1E-26), and CYP11B2 rs1799998 (TT, 9.1%; TC, 8.7%; CC, 1.4%; P = 0.0006) genotypes.
	ADRB1 (rs1801252 and rs1801253)	Boost intracellular response to β1-adrenergic receptor agonists compared to other variant alleles. Patients with the CC genotype may have an increased response to metoprolol as compared to patients with the CG or GG genotype.
	NEDD4L (rs4149601)	A allele carriers are particularly sensitive to HCTZ treatment
	SIGLEC12, A1BG, F5	A genetic risk score, including rs16982743, rs893184, and rs4525 in F5, was significantly associated with treatment-related adverse cardiovascular outcomes in whites and Hispanics from the INVEST study and in the Nordic Diltiazem study (meta-analysis interaction P=2.39×10(-5)). In patients with a genetic risk score of 0 or 1, calcium channel blocker treatment was associated with lower risk (odds ratio [95% confidence interval]=0.60 [0.42-0.86]), and in those with a genetic risk score of 2 to 3, calcium channel blocker treatment was associated with higher risk (odds ratio [95% confidence interval]=1.31 [1.08-1.59]). These results suggest that cardiovascular outcomes may differ based on SIGLEC12, A1BG, F5 genotypes, and antihypertensive treatment strategy.
	FGB-455	Variant allele carriers of the FGB gene at position -455 have a better outcome if randomized to lisinopril than chlorthalidone (for mortality and ESRD) or amlodipine (for mortality and stroke). For

		the models in which a pharmacogenetic effect was observed, the outcome rates among "GG" homozygotes were higher in those randomized to lisinopril versus amlodipine or chlorthalidone.
Antiarrhythmics [174]	CYP2C8*14 (rs188934928)	Genetic polymorphism of the CYP2C8*14 allele influences the clinical response to amiodarone, although there is no information on the relationship between CYP2C8*14 allele and the pharmacokinetics of amiodarone at present.

Supplemental Table 2. Industry Focused on Cardiovascular Genetic Testing *

Company	Test Information
GeneDx (*Stamford, CT)* https://www.genedx.com	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing, and Deletion/Duplication Analysis **CV Testing:** Multiple test panels based on diagnosis **Genetic Counseling Available:** Pre and post testing available
Ambry Genetics (*Aliso Viejo, CA)* https://www.ambrygen.com	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Multiple test panels based on diagnosis **Genetic Counseling Available:** Pre and post testing available
Cincinnati Children's Laboratory of Genetics and Genomics *(Cincinnati, OH)* https://www.cincinnatichildrens.org/service/c/cardiovascular-genetics	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Multiple test panels based on diagnosis **Genetic Counseling Available:** Pre and post testing available
Invitae Genetics Laboratories *(San Francisco, CA)* https://www.invitae.com/en	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Multiple test panels based on diagnosis **Genetic Counseling Available:** Pre and post testing available
Variantyx *(Framingham, MA)* https://www.variantyx.com/	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Whole genome analysis **Genetic Counseling Available:** Pre and post testing available

Nebula Genomics *(San Francisco, CA)* https://nebula.org/whole-genome-sequencing-dna-test/	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Whole genome analysis **Genetic Counseling Available:** Outside referral
CD genomics *(Shirley, NY)* https://www.cd-genomics.com/	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Multiple test panels based on diagnosis **Genetic Counseling Available:** Not available
Helix/MAYO *(San Mateo, California)* https://www.helix.com https://www.mayo.edu/research/centers-programs/center-individualized-medicine/research/clinical-studies/tapestry	**Complexity:** High complexity testing **Platform:** Next-Gen Sequencing **CV Testing:** Whole exome sequencing, IcWGS and microarrays, and targeted panels **Genetic Counseling Available:** Available during and after receiving their results
Genomadix *(Kanata, ON)* https://genomadix.com/	**Complexity:** Moderate complexity testing **Platform:** POC Genomadix Cube System **CV Testing:** CYP2C19*2,3,17 **Genetic Counseling Available:** Not available

*Table does not include all companies, universities, and hospitals that perform genomic testing.