SUPPLEMENT MATERIAL

Actionable Variants Identified by Genome Sequencing: Penetrance and Near-Term Outcomes Following Return to Participants

Lee et al

Table 1: Relevant Family History

Condition	Related Diagnoses	Family history of Related Diagnosis
Familial Hypercholesterolemia n = 18	History of Hyperlipidemia and ASCVD	8
Lynch Syndrome n = 10	History of colorectal or endometrial cancer	4
Hereditary Breast and Ovarian Cancer Syndrome n = 8	History of Breast or ovarian cancer	4
Long Q-T syndrome n=10	History of LQT syndrome diagnosis or prolonged QT interval	0
Cardiomyopathy/ARVC n = 11	History of related cardiomyopathy	2
Hemochromatosis n = 9	History of hemochromatosis	0
Factor V Leiden n = 4	History of recurrent thrombosis	2
CHEK2 n= 2	History of: Breast cancer Prostate cancer Stomach cancer Sarcoma Kidney cancer	2
Familial Adenomatous Polyposis n = 2	History of FAP or extensive polyps or polyps leading to colectomy.	0
PALB2 n = 2	History of breast cancer or pancreatic cancer	0
Multiple Endocrine Neoplasia type IIA n = 2	History of: MEN syndrome Medullary thyroid carcinoma Pheochromocytoma, Parathyroid adenoma/hyperplasia	1
Malignant hyperthermia n = 1	History of malignant hyperthermia diagnosis.	0
MCAD deficiency n = 1	History of MCAD deficiency.	0
Ehlers-Danlos n = 1	History of: Vascular type Ehlers-Danlos syndrome. Arterial aneurysms, dissection, or rupture	1

ARVC= arrhythmogenic right ventricle cardiomyopathy

Table 2. A summary of actionable variants identified during the RAVE study

	Gene	Variant	eMERGE Classification*	Relevant Traits	Manifestation	Comments	Tests Completed
Tier 1 Variants							
Familial Hypercholesterolemia							
1	*LDLR*	c.796G>A (p.Asp266Asn)	LP	+	Hypercholesterolemia, LDL-C 184 mg/dL	Declined referral	—
2	*LDLR*	c.782G>T (p.Cys261Phe)	LP	+	Hypercholesterolemia, LDL-C 206 mg/dL	Seen in FH clinic	Lipid Profile Apo B level Lipoprotein (a)
3	*LDLR*	c.796G>A (p.Asp266Asn)	LP	-	Hypercholesterolemia, LDL-C 146 mg/dL	Statin intolerant, declined referral	—
4	*LDLR*	c.131G>A (p.Trp44*)	P	+	Hypercholesterolemia, LDL-C 218 mg/dL	Referred to FH clinic but did not follow up	Lipid Profile
5	*LDLR*	c.1444G>A (p.Asp482Asn)	LP	+	Hypercholesterolemia, LDL-C 216 mg/dL	Declined referral	—
6	*LDLR*	c.862G>A(p.Glu288Lys)	LP	+	Hypercholesterolemia, LDL-C 198 mg/dL	Declined referral	—
7	*LDLR*	c.1444G>A (p.Asp482Asn)	LP	+	Hypercholesterolemia, LDL-C 217 mg/dL	Opted to see PCP first	Lipid Profile
8	*LDLR*	c.798T>A (p.Asp266Glu)	LP	+	Hypercholesterolemia, LDL-C 218 mg/dL	Referred to FH clinic but did not follow up	Lipid Profile
9	*LDLR*	c.1640T>C (p.Leu547Pro)	LP	+	Hypercholesterolemia, LDL-C 348 mg/dL	Previous Dx of FH (genetic)	Lipid Profile
10	*LDLR*	C.1474G>A (p.Asp492Asn)	LP	+	Hypercholesterolemia, LDL-C 243 mg/dL	Seen in FH Clinic, statin dose increased and ezetimibe started	Lipid Profile ECG Echocardiography Lipoprotein (a) Apo B
11	*LDLR*	c.1432G>A (p.Gly478Arg)	LP	+	Hypercholesterolemia, LDL-C 256 mg/dL	Seen in FH Clinic	Lipid Profile ECG Lipoprotein (a) Apo B
12	*LDLR*	c.1860G>A (p.Trp620*)	P	+	Hypercholesterolemia, LDL-C 303 mg/dL	Declined referral	—
13	*LDLR*	c.796G>A (p.Asp266Asn)	LP	+	Hypercholesterolemia, LDL-C 196 mg/dL	Seen in FH Clinic	Lipid Profile ECG Lipoprotein

							(a) Apo B CT coronary calcium
14	*LDLR*	c.420G>C (p.Glu140Asp)	LP	+	Hypercholesterolemia, LDL-C 280 mg/dL	Previous Dx of FH (genetic) Declined FH clinic referral	—
15	*LDLR*	c.1586+5G>A	LP	+	Hypercholesterolemia, LDL-C 162 mg/dL	Opted to follow with PCP	—
16	*LDLR*	c.1238C>T(p.Thr413Met)	LP	+	Hypercholesterolemia, LDL-C 212 mg/dL	Declined FH clinic referral	—
17	*LDLR*	c.1444G>A (p.Asp482Asn)	LP	+	Hypercholesterolemia, LDL-C 308 mg/dL†	—	Lipid Profile
18	*LDLR*	c.542C>G (p.Pro181Arg)	LP†	-	Hypercholesterolemia, LDL-C 159 mg/dL	—	Lipid Profile
19	*LDLR*	c.2029T>C (p.Cys677Arg)	LP	+	Hypercholesterolemia, LDL-C 236 mg/dL	—	—
20	*APOB*	c.10580G>A (p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 196 mg/dL	—	Lipid Profile
21	*APOB*	c.10580G>A (p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 217 mg/dL	Seen in FH clinic	Lipid Profile ECG Lipoprotein (a) Apo B CT coronary calcium
22	*APOB*	c.10580G>A(p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 308 mg/dL‡	Medications reviewed in FH clinic, PCSK 9 considered if LDL-C does not reach goal	Lipid Profile
23	*APOB*	c.10580G>A(p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 210 mg/dL	Already on high dose statin and ezetimibe Declined referral	Lipid Profile
24	*APOB*	c.10580G>A (p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 347 mg/dL	Previous Dx of FH (genetic)	—
25	*APOB*	c.10580G>A (p.Arg3527Gln)	P	+	Hypercholesterolemia, LDL-C 194 mg/dL	—	Lipid Profile
26	*PCSK9*	c.644G>A (p.Arg215His)	LP	+	Hypercholesterolemia, LDL-C	Seen in FH Clinic	Lipid Profile ECG

					315 mg/dL†		Lipoprotein (a) Apo B CT coronary calcium
FH = Familial Hypercholesterolemia; LDL-C = Calculated Low-Density Lipoprotein cholesterol (maximum level in the EHR); ; Apo B level = Apolipoprotein B; ECG = Electrocardiogram; CT = Cardiac computed tomography; *eMERGE classification matches ClinVar classification unless noted otherwise; † = 3 likely pathogenic, 2 variant of uncertain significance, and 1 likely benign classification in ClinVar; ‡= Corrected LDL-C for lipid lowering therapy.							
Hereditary Breast and Ovarian Cancer Syndrome							
27	*BRCA1*	c.2035A>T (p.Lys679*)	P	+	—	Previous genetic testing for family Hx Previous BM+BSO	—
28	*BRCA1*	deletion of exons 13-15	P	+	Personal history of breast cancer in early 30's	Previous genetic testing Previous BM+BSO	—
29	*BRCA1*	c.5251C>T (p.Arg1751*)	P	+	—	Previous genetic testing Previous BM+BSO	—
30	*BRCA1*	c.3756_3759delGTCT (p.Ser1253Argfs*10)	P	+	—	Previous genetic testing Previous BM+BSO	—
31	*BRCA1*	c.3756_3759delGTCT (p.Ser1253Argfs*10)	P	+	Personal history of breast cancer in mid 40's	Previous genetic testing	—
32	*BRCA1*	c.5109T>G (p.Tyr1703*)	P	-	Strong family history of breast cancer		MRI Breast Mammography
33	*BRCA1*	c.5096G>A (p.Arg1699Gln)	LP	+	—	Previous genetic Dx, previous Lynch Syndrome, previous TAH/BSO. Underwent BM	—
34	*BRCA2*	c.5217_5223delTTTAAGT (p.Tyr1739*)	P	+	—	BM+BSO after RoR	MRI breast US pelvis CA 125 level
35	*BRCA2*	c.8168A>C (p.Asp2723Ala)	LP	+	—	Previous genetic testing, previous BM+BSO	—

36	*BRCA2*	c.1813dup (p.lle605Asnfs*11)	P	+	Personal history of Breast cancer in mid 40's	Previous genetic testing Previous BM +BSO	—
37	*BRCA2*	c.6033_6034delTT (p.Ser2012Glnfs*5)	P	-	—	Male referred to high risk breast clinic but did not follow up	—
38	*BRCA2*	c.4472_4475delTGAA (p.Leu1491Glnfs*12)	P	+	—	Previous genetic testing Previous BM	—
39	*BRCA2*	c.8243G>A (p.Gly2748Asp)	P	-	—	Male, followed by PCP	PSA
40	*BRCA2*	c.6842-2A>G	LP	+	Personal history of prostate cancer in mid 60's	Male	PSA
41	*BRCA2*	c.3847_3848del (p.Val1283Lysfs*2)	P	-	—	Male, followed by PCP	PSA Prostate Exam
42	*BRCA2*	c.6275_6276delTT (p.Leu2092Profs*7)	P	+	—	Previous TAH BSO for benign tumor Underwent BM based on ROR	MRI breast
43	*BRCA2*	9294C>G (p.Tyr3098*)	P	-*	—	PCP Male	Surveillance: Yearly clinical breast exam PSA Prostate Exam
BM = Bilateral Mastectomy; BSO = Bilateral Salpingo-Oophorectomy; TAH = Total Abdominal Hysterectomy; MRI = Magnetic Resonance Imaging; US = Ultrasound; CA 125 = cancer antigen 125;*developed prostate cancer but > 1-year post RoR.							
Lynch Syndrome							
44	*MSH6*	c.2731C>T (p.Arg911*)	P	-	Colon polyps	Previous Dx Lynch Syn. (genetic)	—
45	*MSH6*	c.3261_3262insC (p.Phe1088Leufs*5)	P	-	—	PCP follow-up Prior hysterectomy and BSO due to endometriosis	EGD Colonoscopy
46	*MSH6*	c.32012C>T (p.Arg1068*)	P	-	—	Referred to GI neoplasia clinic	—

						(pending)	
47	*MSH2*	Deletion Exons 1-3	P	+	Personal history of colorectal cancer in early 30's Paternal aunt had uterine cancer in mid 20's	Previously known genetic Dx	—
48	*MSH2*	Del Exons 4-6	P	+	Personal history of endometrial cancer in early 40's	Previously known genetic Dx	—
49	*PMS2*	c823C>T (p.Gln275*)	P	-	Colon polyps	Referral to GI clinic	EGD Colonoscopy PSA
50	*PMS2*	c.2117delA (p.Lys706Serfs*10)	P	-	—	TAH/BSO after RoR	Colonoscopy CT enterography CT abdomen Urine cytology
51	*PMS2*	c.325dup (p.Glu109Glyfs*30)	P	-	—	Previous TAH/BSO for uterine fibroids	EGD Colonoscopy Pelvis U/S
52	*PMS2*	c.614A>C (p.Gln205Pro)	LP*	-	Hyperplastic colon polyps	Declined referral or further testing	—
53	*PMS2*	c.1939A>T (p.Lys647*)	P	-	—	GI neoplasia Clinic for ongoing management	Colonoscopy
54	*PMS2*	c.736_741delinsTGTGTGTGAAG (p.Pro246Cysfs*3)	P	-	—	TAH+BSO after RoR	Transvaginal US Endometrial sampling Colonoscopy EGD
55	*PMS2*	c.400C>T (p.Arg134*)	P	-	—	Male Referred to the GI neoplasia clinic for further management	Colonoscopy EGD
56	*PMS2*	c.2113G>A (p.Glu705Lys)	LP	-	—	Female TAH+BSO based on RoR	Urine cytology Yearly colonoscopy
57	*PMS2*	c.1021delA (p.Arg341Glyfs*15)	P	+	Personal history of ovarian cancer (early 40's)	Female	—
58	*MLH1*	c.677G>T (p.Arg226Leu)	LP	-	—	Male	—

CT = Computed tomography; TAH = total abdominal hysterectomy; BSO = bilateral salphingo-oophorectomy; EGD = esophagogastroduodenoscopy; LP* = 3 Likely pathogenic and 3 variant of uncertain significance classifications in ClinVar							
Non-Tier 1 Variants							
Familial Adenomatous Polyposis							
59	*APC*	c.694C<T (p.Arg232*)	P	+	FAP diagnosis	Previous clinical Dx of FAP	—
60	*APC*	c.3920T>A (p.lle1307Lys)	Risk Factor	-	Few adenomatous polyps, one with low grade dysplasia	Female in her late 60's. No referral needed	Colonoscopy every 5 years
61	*APC*	C.1262G>A (P.Trp421Ter)	P	-	Previously normal colonoscopy	Presumed mosaic	Endoscopy
FAP = Familial Adenomatous Polyposis							
Hypertrophic Cardiomyopathy							
62	*TNNI3*	c.497C>T (p. Ser166Phe)	P	+	Hypertrophic cardiomyopathy diagnosis; Sigmoid ventricular septum with basal septal prominence (14 mm)	Seen in Hypertrophic Cardiomyopathy Clinic	cMRI ECG EST Echocardiogram 24-h Holter
63	*TNNI3*	c.484C>T (p.Arg162Trp)	P	-	—	Seen in Hypertrophic Cardiomyopathy Clinic	Echocardiogram Strain ECG
64	*MYPBC3*	c1504C>T (p.Arg502Trp)	P	-	—	Seen in Hypertrophic Cardiomyopathy Clinic	cMRI Standard ECG Echocardiogram
65	*MYPBC3*	c1504C>T (p.Arg502Trp)	P	-	—	Seen in Hypertrophic Cardiomyopathy Clinic	Standard ECG Echocardiogram Signal-averaged ECG 24-h Holter
66	*MYPBC3*	c.905+1G>T	LP	-	—	Declined referral to the Hypertrophic Cardiomyopathy Clinic	—
67	*MYH7*	c.4499G>A (p.Arg1500Gln)	LP	-	—	Referred to Hypertrophic Cardiomyopathy clinic but did not	—

						follow up	
68	*MYL3*	c.170C>G	LP*	-	—	Seen in Hypertrophic Cardiomyopathy Clinic, also found to have *SCN5A* P variant	ECG Echocardiogram EST
cMRI = Cardiac Magnetic Resonance Imaging; ECG = Electrocardiogram; EST = Exercise stress test; * Downgraded later to VUS by eMERGE							
Arrhythmogenic Right Ventricular Cardiomyopathy							
69	*DSC2*	c.2125+1del	LP	-	—	Referred to cardiology	cMRI ECG EST Echocardiogram 24-h Holter
70	*PKP2*	c.275T>A (p.Leu92*)	P	-	—	Referred to cardiology	cMRI ECG EST Signal-averaged ECG 24-h Holter
71	*PKP2*	c.1162C>T (p.Arg388Trp)	LP	-	Previous ECG and echocardiogram normal	Declined referral	—
72	*PKP2*	c.235C>T (p.Arg79*)	P	-	—	—	—
73	*DSP*	c.597_598insGTAA (p.Arg199fs)	LP	-	—	Referred to cardiology	ECG Signal-averaged ECG 24-h Holter
74	*DSP*	c.2794-2A>T	LP	-	—	—	—
cMRI = Cardiac Magnetic Resonance Imaging; ECG = Electrocardiogram; EST = Exercise stress test; ECHO = Echocardiogram; EP = Electrophysiology							
Long QT/Brugada Syndrome							
75	*KCNQ1*	c.1893dup (p.Arg632GInfs*20)	P	-	Normal QTc interval (QTc= 401 ms - 434 ms)	Referred to EP clinic but was not seen	—
76	*KCNQ1*	c.1552C>T (p.Arg518*)	P	+	QTc interval (QTc= 455 ms - 517 ms)	—	ECG Echocardiogram 24-h Holter EST
77	*KCNQ1*	c.944A>G (p.Tyr315Cys)	LP	+	QTc interval (QTc= 412 ms - 490 ms)	Previously diagnosed in EP clinic	—
78	*KCNQ1*	Del exons 4-7	P	+	QTc interval (QTc= 453 ms -	—	ECG Echocardiogra

					484 ms)		m 24-h Holter EST
79	*KCNQ1*	c.776G>A (p.Arg259His)	LP	-	QTc interval (QTc= 443 ms - 453 ms), Male	Awaiting EP Review	—
80	*KCNQ1*	c.905C>T (p.Ala302Val)	LP	-	—	—	—
81	*KCNE1*	c.226G>A (p.Asp76Asn)	LP	+	QT interval (QTc= 420 ms - 519 ms)	Nadolol started	ECG, EST
82	*KCNE1*	c.292C>T (p.Arg98Trp)	P*	+	QT interval (QTc= 447 ms - 495 ms)	Seen by specialist	ECG Echocardiogram 24-h Holter EST
83	*SCN5A*	c.4886G>A(p.Arg1629Gln)	LP	-	No ECG finding consistent with Brugada syndrome	—	ECG Brugada-protocol ECG Echocardiogram EST
84	*SCN5A*	c.3956G>T (p.Gly1319Val)	P	-	No ECG finding consistent with Brugada syndrome	—	Brugada-protocol ECG 24-h Holter EST
85	*KCNH2*	c.1468G>A (p.Ala490Thr)	P	-	QT interval (QTc= 397 ms - 466 ms)	Referred EP clinic but not seen	—
86	*KCNH2*	c.446dupG (p.Thr152Hisfs*180)	LP	+	QT interval (QTc= 474 ms - 540 ms)	Previously known to EP	No change in Mx Previous genetic Dx
87	*KCNH2*	c.2762delG (p.Gly921Alafs*53)	LP	+	QT interval (QTc= 482 ms - 509 ms)	Seen in EP clinc	ECG 24-h Holter EST
ECG = Electrocardiogram; EST = Exercise stress test; TTE = Trans-thoracic Echocardiogram; EP =Electrophysiology; Mx = Management; P* = 1 pathogenic, 1 likely pathogenic, and 2 variant of uncertain significance classifications in ClinVar							
Marfan Syndrome and Vascular Ehlers-Danlos Syndrome							
88	*FBN1*	c.2495G>A (p.Cys832Tyr)	P	+	Marfan Syndrome	Clinical Dx of Marfan Syndrome	—
89	*COL3A1*	c.4087C>T (p.Arg1363*)	LP	-	Previous MRI brain didn't show aneurysms	Referred to Clinical Genomics but did not follow up Daughter has spontaneous coronary artery dissection and two vertebral	—

						aneurysms	
Hereditary Hemochromatosis							
90	*HFE*	c.845G>A (p.Cys282Tyr)	P	-	Ferritin = 201 ng/mL	PCP referral	—
91	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 83 ng/mL, Transferritin SAT = 58%)	Started therapy	Ferritin MRI Liver
92	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 405 ng/mL, Transferritin SAT = > 90 %)	Seen by gastroenterology and started therapeutic phlebotomy	Iron studies, Liver Enzymes, Liver Elastogram w/o contrast
93	*HFE*	c.845G>A (p.Cyc282Tyr)	P	+	(Ferritin = 560 ng/mL, Transferritin SAT = 74%)	PCP Referral	Annual transferrin saturation and ferritin level monitoring
94	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 444 ng/mL, Transferritin SAT = 72%)	Started therapy	Ferritin MRI Liver
95	*HFE*	c.845G>A (p.Cys292Tyr)	P	+	Ferritin = 293 ng/mL	—	Previous clinical diagnosis and genetic testing
96	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 195 ng/mL, Transferritin SAT = 68%)	Referred to gastroenterology but not yet seen	Iron studies
97	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 904 ng/mL, Transferritin SAT = 68%)	Started therapy	Iron studies
98	*HFE*	c.845G>A (p.Cys282Tyr)	P	-	Ferritin = 67 ng/mL	PCP surveillance	—
99	*HFE*	c.845G>A (p.Cys282Tyr)	P	-	(Ferritin = 150 ng/mL, Transferritin SAT = 50%)	PCP surveillance	Normal ferritin and transferrin
100	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 2 ng/mL, Transferritin SAT = 6%)	Previous clinical diagnosis, previous therapy	—
101	*HFE*	c.845G>A (p.Cys282Tyr)	P	-	(Ferritin = 109 ng/mL, Transferritin SAT = 34%)	Previously known	—
102	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 156 ng/mL, Transferritin SAT = 59%)	Previously known	—

103	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 133 ng/mL, Transferritin SAT = 62%)	Previously known	—
104	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 230 ng/mL, Transferritin SAT = > 90%)	Previously known	—
105	*HFE*	c.845G>A (p.Cys282Tyr)	P	+	(Ferritin = 195 ng/mL, Transferritin SAT = 73%)	Previously known	—
MRI = Magnetic Resonance Imaging							
Malignant Hyperthermia							
106	*RYR1*	c.1840C>T (p.Arg614Cys)	P	-	No previous anesthesia complications (Succinylcholine was used)	EHR alert was implemented to alert anesthesiologist	—
Medium-Chain Acyl-CoA Dehydrogenase Deficiency							
107	*ACADM*	c.997A>G (p.Lys333Glu)	P	-	—	Referred to medical geneticist but did not follow up	—
Multiple Endocrine Neoplasia Type II							
108	*RET*	c.2410G>A (p.Val804met)	P	-	—	Seen by endocrinology	US Thyroid, PTH, Vit-D, Calcitonin, 24hr urine C/M
109	*RET*	c.23705>T(p.Leu790Phe)	P	-	—	Seen by endocrinology	US Thyroid, PTH, Vit-D, Calcitonin, 24hr urine C/M
US = Ultrasound; PTH = Parathyroid hormone; C/M = Catecholamines and Metanephrines							
Factor V Leiden							
110	*F5*	c.1601G>A (p.Arg534Gln)	P	-	No Hx of VTE	Also found to have *RET* P variant	—
111	*F5*	c.1601G>A(p.Arg534Gln)	P	+	Hx of DVT	Hx DVT, referred to thrombophilia clinic and started prophylactic rivaroxaban	—
112	*F5*	c.1601G>A(p.Arg534Gln)	P	-	No Hx of VTE	PCP referral	—
113	*F5*	c.1601G>A; (p.Arg534Gln)	P	-	No Hx of VTE	PCP referral No Hx	—

						DVT/PE	
DVT = Deep vein thrombosis; VTE = Venous thromboembolism; PE = Pulmonary embolism							
Breast and Pancreatic Cancer Risk							
114	*PALB2*	c.172_175delTTGT (p.Gln60Argfs*7)	P	-	Hx of CRC Mother had breast cancer in late 40's	Male with Hx of CRC Referred to Gastroenterology	Colonoscopy Urine cytology MRCP (ordered but not completed) CA 19-9
115	*PALB2*	c.2748+1G>T	LP	+	Personal history of breast cancer (WLE, tamoxifen)	Referred to Breast clinic New genetic Dx	Bilateral breast screening with tomosynthesis
CRC = Colorectal cancer; WLE = Wide Local Excision							
Cancer Risk							
116	*CHEK2*	Del Exons 9-10	P	+	Personal history of breast cancer early 50's	Seen in Breast clinic	Breast MRI Yearly mammogram
117	*CHEK2*	Del Exons 1-15	P	+	Personal history of prostate cancer in mid 40's	Male No referral already being followed	Colonoscopy every 5 years
Hypokalemic Periodic Paralysis							
118	CACNA1S	c.1583G>A (p.Arg528His)	P	+	Previous Clinical Dx of hypokalemic periodic paralysis	—	—

FH = Familial Hypercholesterolemia; P = Pathogenic; LP= Likely Pathogenic; BM = Bilateral mastectomy; BSO = Bilateral Salpingo-oophorectomy; HCM = Hypertrophic cardiomyopathy, ARVC = Arrhythmogenic right ventricular cardiomyopathy, LQTS = Long QT Syndrome; P* or LP* indicate that the eMERGE classification differed from consensus classification in ClinVar (B+LB+VUS classifications ≥ P+LP classifications).

Table 3. Criteria for ascertaining penetrance

Gene	Clinical diagnosis	Test Findings
LDLR, PCSK9, APOB	Familial Hypercholesterolemia	LDL >= 190 off cholesterol medications / > 160 on cholesterol medications
BRCA1 BRCA2	HBOC	Previous Diagnosis of breast or ovarian cancer
PMS2	Lynch Syndrome	Previous diagnosis of cancer
MYPBC3 MYH7 MYL3 TNNI3	Hypertrophic/ Dilated Cardiomyopathy	Echocardiography with posterior LV, posterior wall thickness, or SW >12 mm, or echocardiography with LV diastolic diameter >6 cm and fractional shortening <20%
DSC2 PKP2 DSP	ARVC	Echocardiography with abnormal RV or RA appearance
KCNQ1 KCNE1 KCNH2	LQT Syndrome	ECG showing Q-T interval > 460 ms in female and > 450 ms in males
SCN5A	LQT Syndrome or Brugada Syndrome	ECG showing Brugada type I pattern
CACNA1S	Hypokalemic Periodic Paralysis	Potassium level < 3.6 mmol/L with Periodic Paralysis
PALB2	Breast, Ovarian or Pancreatic Cancer	MRI, CT scan, Mammogram or US evidence of related cancer
CHEK2	Breast or Prostate Cancer	MRI, CT scan, Mammogram or US evidence of related cancer
APC	Familial Adenomatous Polyposis	MRI, CT scan, colonoscopy or US findings suggestive of FAP
RET	MEN or associated tumors	MRI, CT scan, or US findings suggestive MEN syndrome related neoplasia or lung cancer

HFE Homo	Hemochromatosis	Ferritin level > 200 ng/ml or Tranferritin SAT > 50%, Iron > 150 mcg/dL, TIBC < 250 mcg/dL MRI, CT scan, or US findings suggestive of iron depositions
F5	Factor V Leiden or thrombophilia	History of multiple venous thrombosis
COL3A1	Ehlers-Danlos syndrome	Imaging evidence of related arterial aneurysm or dissection.
FBN1	Marfan Syndrome	Dilated aortic root on imaging
ACADM	MCAD deficiency	—
RYR1	Malignant Hyperthermia	History of malignant hyperthermia with anesthesia

HBOC= Hereditary Breast and Ovarian Cancer; ARVC = arrythmogenic right ventricular cardiomyopathy; LQTS = long QT syndrome; ECG = electrocardiogram; MRI = magnetic resonance imaging; US = ultrasound; CT = computed tomograph; CA 125 = cancer antigen 125; FAP = familial adenomatous polyposis; Tranferritin SAT = tranferritin saturation; TIBC = total iron binding capacity

Table 4. 1-year Outcomes after Return of Results: In participants with previously known diagnoses [1]

	Overall n=18	**Tier 1 n=12**	**non-Tier 1 n=6**	***P***
Age, years	59.6 ± 6.9	59.8 ± 8	59.3 ± 1.5	0.8
Female	14 (77.8)	10 (83.3)	4 (66.6)	0.56
Family history	14 (77.8)	12 (100)	2 (33.3)	0.0049
Any outcome	16 (88.2)	12 (100)	4 (66.6)	0.09
Process Outcomes	16 (88.2)	12 (100)	4 (66.6)	0.09
Referral to a specialist	14 (77.8)	11 (91.7)	3 (50)	0.083
Investigations based on RoR	15 (83.3)	11 (91.7)	4 (66.6)	0.24
Surveillance initiated	9 (50)	8 (66.7)	1 (16.6)	0.13
Intermediate Outcomes	15 (83.3)	12 (100)	3 (50)	0.024
New tests finding	6 (33.3)	3 (25)	3 (50)	0.34
New diagnosis	14 (77.7)	11 (91.7)	3(50)	0.08
Clinical Outcomes	12 (70.6)	8 (66.6)	4 (66.6)	1
Risk reduction surgery	8 (44.4)	8 (66.7)	0	0.012
Medication or therapy started/altered	5 (27.8)	1 (8.3)	4 (66.6)	0.021

Age is presented as mean ± standard deviation; the remaining features are presented as n (percentage)

Detailed description of outcomes

Tier 1 conditions

Familial Hypercholesterolemia (FH) (*LDLR, APOB, PCSK9*). FH variants were returned to 18 participants who were not previously aware of a genetic diagnosis. Each carried a previous diagnosis of hypercholesterolemia, however only one was previously diagnosed with FH. In those already diagnosed with hypercholesterolemia, RoR prompted further investigations (n=10), modifications to therapy (n=3) or periodic surveillance (n=4) **(Table 3 and Figure 1)**. Tests performed based on RoR included lipid panel (n=9), apolipoprotein B (n=6), lipoprotein(a) (n=5), ECG (n=7), stress echocardiogram (n=2) and CT coronary calcium scan (n=4). Changes in the drug therapy included starting/restarting a statin (n=1), increasing statin dosage (n=1), and adding ezetimibe (n=1). Referral to the FH clinic was declined by 9 participants who were already being managed for hypercholesterolemia by their respective primary care physician or specialist.

Table 5. Outcomes in participants with FH P/LP variants

	Process Outcomes ***n = 10***			***Clinical Outcomes*** ***n = 3***
Gene ***(18 Participants)***	**Referred to Specialist n = 9**	**Tests Performed n = 10**	**Surveillance n = 4**	**Change in Therapy n = 3**
LDLR n = 14 6 male 8 female	6	(7 participants) Lipid Panel (6) ECG (5) Lipoprotein (a) (3) Apo B (4) CT Coronary Calcium (2) Stress Echo (2)	2	Statin dose increased (1) Ezetimibe started (2)
APOB n = 3 2 male 1 female	2	(2 participants) Lipid Panel (2) Lipoprotein (a) (1) Apo B (1) CT Coronary Calcium (1) ECG (1)	1	
PCSK9 n = 1 Female	1	Lipid Panel (1) Lipoprotein (a) (1) Apo B (1) CT Coronary Calcium (1) ECG (1)	1	

FH = familial hypercholesterolemia; Apo B = Apolipoprotein B; ECG = electrocardiogram; Echo = echocardiogram

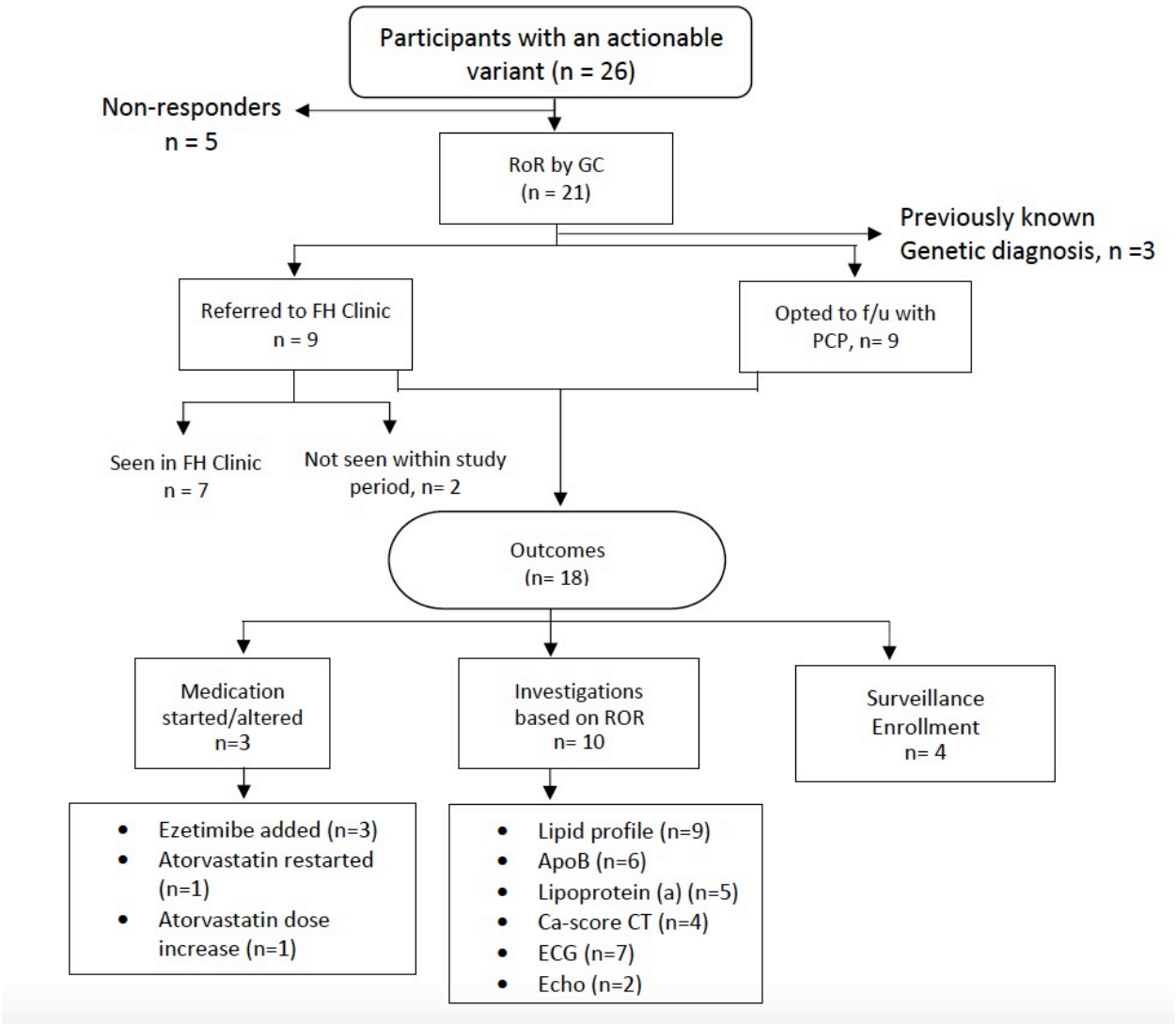

Figure 1. Outcomes in 26 participants with P/LP Familial Hypercholesterolemia (FH) variants

RoR= return of results; GC = genetic counselor; f/u = follow up; PCP = primary care provider; FH = familial hypercholesterolemia; Apo B = Apolipoprotein B; Ca-score CT = Computed tomography coronary calcium; ECG = electrocardiogram; Echo = echocardiogram

Lynch Syndrome. Lynch syndrome variants were returned to 10 participants who did not previously know their result: *MSH6* (n=2) and *PMS2* (n=8) **(Table 4 and Figure 2)**. Within the year after RoR, 7 of these participants had a colonoscopy and 3 female participants underwent prophylactic hysterectomy and bilateral salphingo-oophorectomy (BSO). Of the two participants with a P/LP *MSH6* variant, one had previous bilateral BSO due to endometriosis and opted to follow with her PCP for further management. The second was referred to the high-risk gastrointestinal neoplasia clinic but had yet to complete the follow-up. Of 8 participants with P/LP *PMS2* variants, 5 female participants were referred to a high-risk gastrointestinal neoplasia clinic and to a high-risk gynecology clinic. One participant canceled her referral and saw her PCP instead. Three participants underwent hysterectomy and BSO. One had previously undergone a hysterectomy and bilateral BSO due to endometriosis not related to genetic testing. These participants completed colonoscopy (n=3), transvaginal pelvic ultrasound (n=2), urine cytology (n=2), and were enrolled in yearly surveillance colonoscopy and urine cytology. Of the 3 male *PMS2* participants, 1 declined referral and the remaining 2 were enrolled in yearly surveillance colonoscopy and urine cytology.

Table 6. Outcomes in participants with Lynch Syndrome P/LP variants

	Process Outcomes ***n = 9***			***Clinical Outcomes*** ***n = 3***
Gene (10 Participants)	**Referred to Specialist n = 9**	**Tests Performed n = 8**	**Surveillance n = 8**	**Risk Reduction surgery n = 3**
MSH6 n= 2 *1 Male* *1 Female*	2	(1 participant) Colonoscopy (1) Upper Gastrointestinal endoscopy (1)	1	0
PMS2 n= 8 3 Male 5 Female	7	(7 participants) Colonoscopy (6) Transvaginal Pelvic Ultrasound (2) Urine Cytology (2)	7	Hysterectomy and bilateral salphingo-oophorectomy (3)

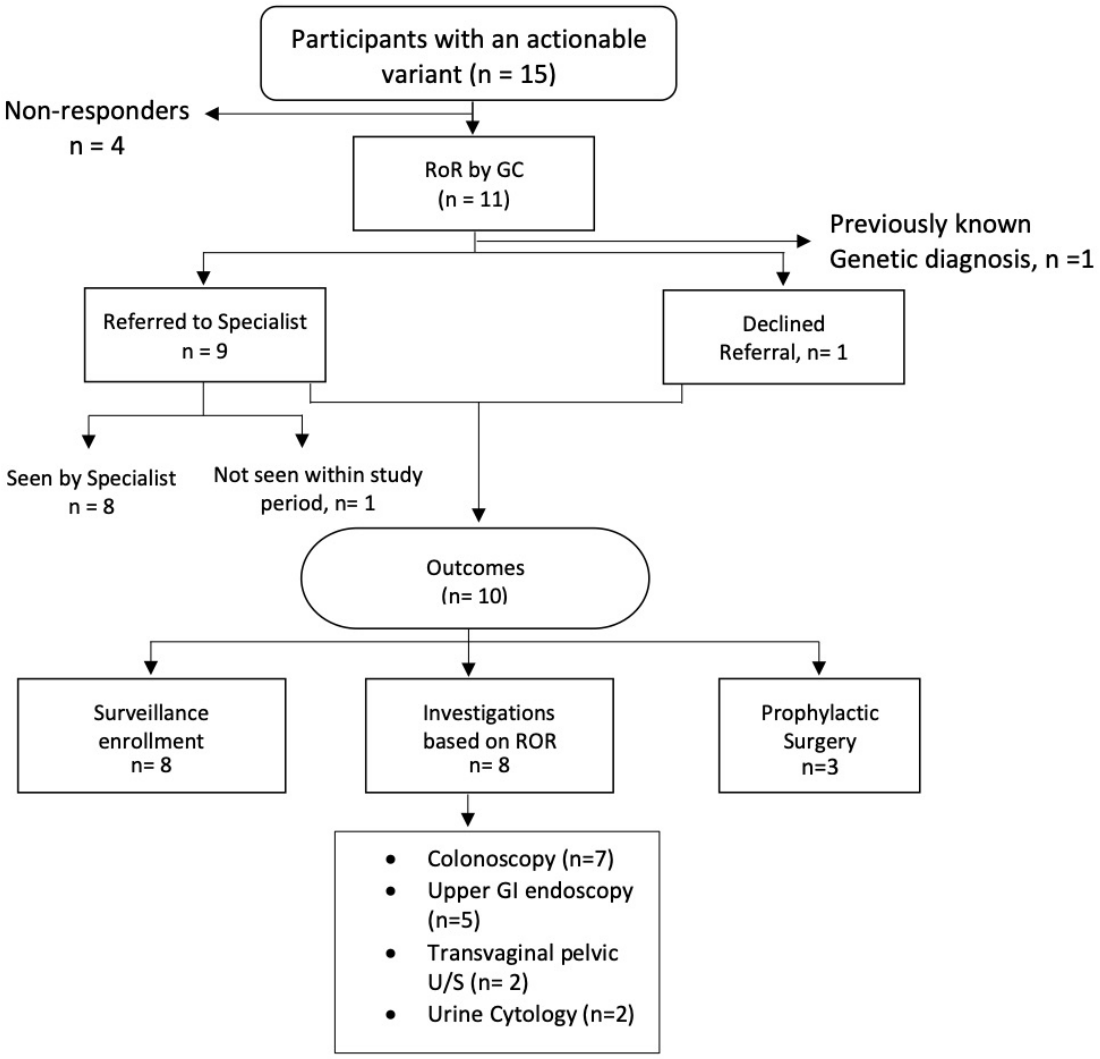

Figure 2. Outcomes in 15 participants with P/LP Lynch Syndrome variants
RoR= return of results; GC = genetic counselor; GI= gastrointestinal

Hereditary Breast and Ovarian Cancer (HBOC)
HBOC variants (*BRCA1, BRCA2*) were returned to 8 participants who did not previously know their result (3 females and 5 males) **(Table 5 and Figure 3)**. All 3 female participants underwent prophylactic surgery based on RoR. One *BRCA1* participant (c.5109T>G) had a previous unrelated hysterectomy and BSO for a Lynch syndrome diagnosis and completed bilateral mastectomy based on RoR. The 2 remaining female *BRCA2* participants both underwent BSO and bilateral mastectomy. Of the 5 male participants, 3 were referred to a specialist and 2 opted to see their PCP instead. Of the male participants, 2 underwent prostate cancer screening tests including prostate rectal exam and PSA.

Table 7. Outcomes in participants with HBOC Syndrome P/LP variants

	Process Outcomes n = 6			***Clinical Outcomes n = 3***
Gene (9 participants)	**Referred to Specialist n = 5**	**Tests Performed n = 6**	**Surveillance n = 6**	**Risk Reduction surgery n = 3**
BRCA1 n= 1 *1 Female*	1	(1 participant) Mammogram (1) MRI Breast (1)	1	1 Mastectomy (1)
BRCA2 n= 7 5 Male 2 Female	4	(5 participants) MRI Breast (2) Ca 125 (1) Pelvic US (1) PSA (2)	5	2 Mastectomy (2)

CA 125 = cancer antigen 125; US = ultrasound; PSA = prostate specific antigen

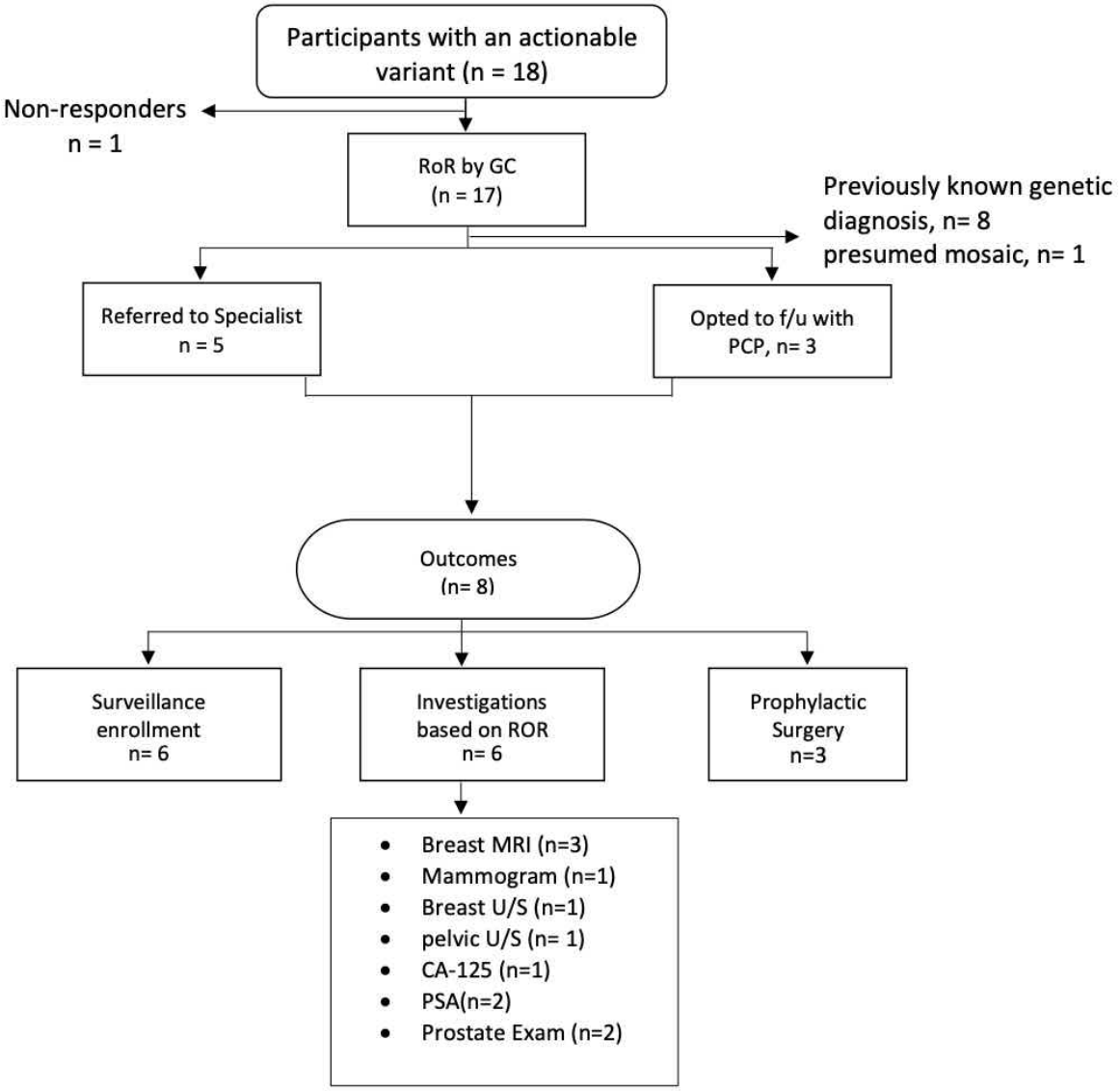

Figure 3. Outcomes in 18 participants with P/LP HBOC Syndrome variants

RoR= return of results; GC = genetic counselor; f/u = follow up; PCP = primary care provider; MRI= magnetic resonance imaging; U/S= ultrasound; CA 125 = cancer antigen 125; US = ultrasound; PSA = prostate specific antigen

Non-Tier 1 conditions

Long QT-Syndrome and Brugada Syndrome. P/LP arrhythmia variants were returned to 10 participants who did not previously know their result: (*KCNQ1 (n=4), KCNE1(n=2), SCN5A(n=2) and KCNH2 (n=2))* **(Table 6 and Figure 4)**. Of the *KCNQ1* variants, one (c.1552C>T) underwent testing (ECG, 24h Holter, echocardiogram, exercise stress test) and had a prolonged QT consistent with LQTS. A second participant (Del Exons 4-7) underwent similar testing but was deemed non-penetrant. Of the remaining two, one (c.776G>A) had been previously identified as having LQTS and was known to the EP clinic, the other participant (c.1893dup) had multiple normal ECG tracings and was referred to EP clinic but had not been seen during the study follow-up period. None of those four participants had an indication of the disease in their family. Two participants with P/LP *KCNE1* variants had QT prolongation on previous ECGs and were referred to an electrophysiologist. One (c.292C>T) was started on a β-blocker by the electrophysiologist (having a family history of asymptomatic prolonged Q-T interval in her mother and of an aunt who died in infancy) and precautionary measures were advised for the other (c.226G>A) whose family history was remarkable for paternal uncle who died in childhood. Both *SCN5A* (Type 1 Brugada/Type 3 LQTS) variant positive participants (c.4886G>A) and (c.3956G>T) were assessed by an electrophysiologist. Triplicate ECGs with the Brugada protocol as well as a 24-h Holter monitor showed no evidence of Brugada patterns in both participants. The participant with (c.4886G>A) had a family history of sudden death in one of her cousins in his 50s, however no pertinent family history was present in the other participant (c.3956G>T). It was felt that QT precautionary measures were not necessary however they were advised to follow Brugada precautions including avoidance of Brugada-aggravating medications, fever reduction and avoidance, as well as avoidance of excess alcohol and drugs such as marijuana and cocaine. One participant with a *KCNH2* variant (c.2762delG) was referred to EP clinic and underwent ECG, echocardiogram and Holter monitor, and was found to have a prolonged QT interval and notched T waves consistent with Long-QT syndrome type 2. Her medications were reviewed and found to be safe for her condition. Her family history was positive for asymptomatic prolongation of QT interval in her mother. She was advised to follow preventative measures include water and electrolyte replenishment especially in the setting of vomiting or diarrhea. Follow-up appointments were scheduled after 3 and 6 months. The other participant with *KCNH2* variant (c.1468G>A) had borderline Q-T prolongation on previous ECGs, she was referred to the EP clinic but had not been seen in the follow-up period. Her family history was unremarkable.

Table 8. Outcomes in participants with Long QT/Brugada Syndrome P/LP variants

	Process Outcomes n = 9			***Clinical Outcomes n = 1***
Gene (10 Participants)	**Referred to Specialist n = 9**	**Tests Performed n = 8**	**Surveillance n = 1**	**Change in Therapy n = 1**
KCNQ1 n = 4 2 male 2 female	4	(4 participant) Exercise Test (2) ECG (4) 24h Holter (2) Echocardiogram (2)	0	0
KCNE1 n = 2 2 female	2	(1 participants) Exercise Test (1) ECG (1)		1 Nadolol started (1)

SCN5A n = 2 2 female	2	(2 participants) 24h Holter (2) ECG (2) Brugada Protocol ECG (2) Signal-Averaged ECG (2) Exercise Test (1) Echocardiogram (1)	0	0
KCNH2 n = 2 2 female	1	(1 participants) 24h Holter (1) ECG (1) Exercise Test (1) Echocardiogram (1)	0	

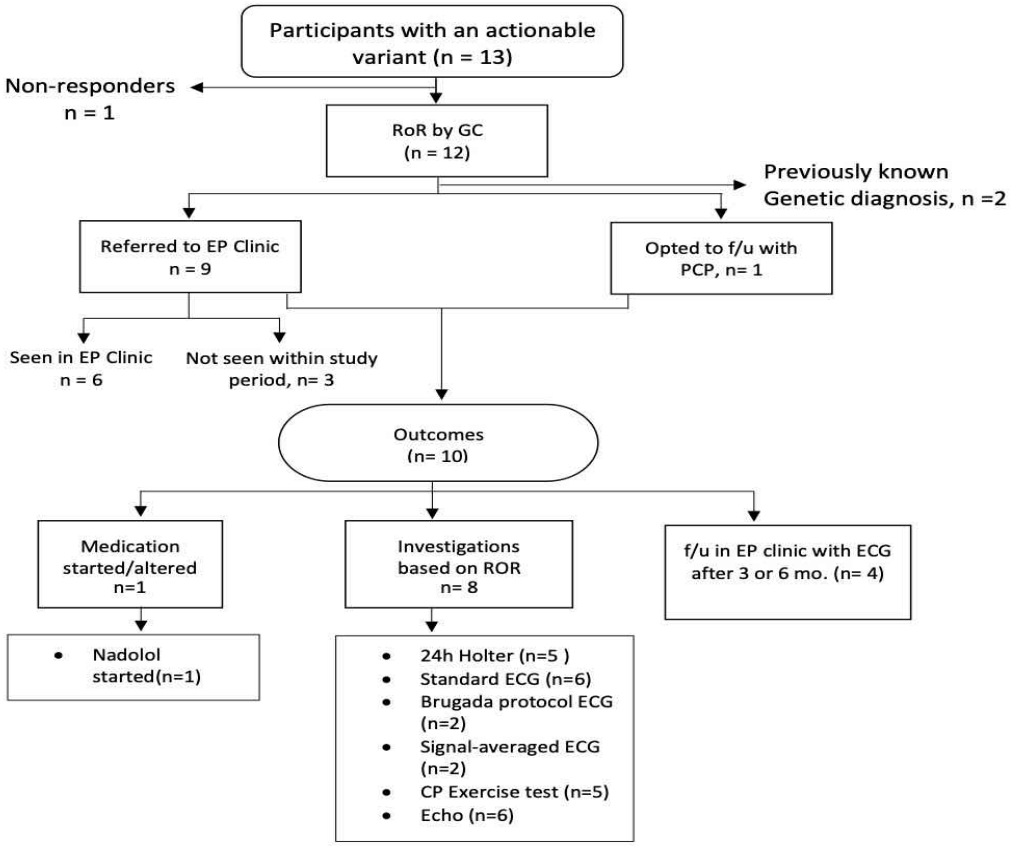

Figure 4. Outcomes in 13 participants with P/LP Long-QT/Brugada Syndrome variants
RoR= return of results; GC = genetic counselor; f/u = follow up; PCP = primary care provider; EP= electrophysiology; ECG = electrocardiogram; CP= cardiopulmonary; Echo = echocardiogram

Cardiomyopathy. Seven participants had P/LP variants associated with cardiomyopathy: *MYBPC3* (n=3), *TNNI3* (n=2), *MYH7* (n=1), *MYL3* (n=1). Two participants with the *MYBPC3* (c.1504C>T) variant underwent ECG and echocardiogram, and one completed cardiac MRI. No phenotypic manifestations of hypertrophic cardiomyopathy were noted and both participants were recommended periodic surveillance with echocardiograms. The remaining participant with *MPBPC3 (*c.905+1G>T) was referred to the Hypertrophic Cardiomyopathy clinic, but declined follow-up, and no related phenotypic data were available in the EHR. A participant with a *TNNI3* variant (c.497C>T) underwent an ECG, echocardiogram and cardiac MRI and was noted to have nonspecific T-wave ECG changes and a thickened basal septum (14 mm) on MRI. There was no family or personal history of syncope or sudden cardiac death. He was initiated on β-blocker therapy and recommended yearly echocardiograms. Another *TNNI3* participant with the c.484C>T variant underwent an ECG and echocardiogram with strain measurement, which were normal, and the variant was deemed to be non-penetrant. It was concluded that this participant did not require further follow-up unless he developed any cardiac symptoms. A participant with an *MYH7* variant (c.4499G>A) had previous normal ECGs and echocardiograms and was referred to hypertrophic cardiomyopathy clinic for further investigations. Evaluation was not completed in the follow-up period. A participant in her mid 60's with a pathogenic (later downgraded to VUS) *MYL3* variant (c.170C>G) had previous normal echocardiograms and was referred to hypertrophic cardiomyopathy clinic for further investigations. She had a family history of sudden death in one of her cousins. Given her normal tests and lack of symptoms, it was determined that the risk of MYL3-mediated cardiomyopathy is extremely low in this patient. No precautionary measures were recommended.

Arrhythmogenic Right Ventricular Dysplasia (ARVC). Four participants had P/LP variants returned which were associated with ARVC in the form of *DSC2* (1), *DSP* (1) and *PKP2* (2). The first *PKP2* participant (c.275T>A) was referred to the arrhythmia clinic and underwent ECG, exercise stress testing, echocardiogram and cardiac MRI; no abnormalities were detected but longitudinal three-yearly surveillance with repeat ECG, echocardiogram, exercise stress test and cardiac MRI was recommended. The second *PKP2* participant (c.1162C>T) was noted to have a previously normal ECG and echocardiogram and declined referral to EP clinic. The *DSC2* participant (c.2125+1del) was seen by an electrophysiologist and underwent an ECG, echocardiogram, exercise stress test and cardiac MRI; all testing was within normal limits. The patient was enrolled in longitudinal five-yearly surveillance with repeat testing. The *DSP* participant (c.597_598insGTAA) was referred to cardiovascular specialist and in addition to ECG, he underwent signal-averaged ECG, 24-h Holter monitor, echocardiogram and exercise stress test. His Holter monitor showed 4 episodes of atrial fibrillation. Upon review in EP clinic, no signs of ARVC were identified and his atrial fibrillation was thought to be unrelated to his genetic results. He continued to follow up with his cardiologist for management of atrial fibrillation and was started on beta-blockers. No anticoagulation was initiated since the CHADS2VASC was 1.

Table 9. Outcomes in participants with Cardiomyopathy P/LP variants

	Process Outcomes ***n = 8***			***Clinical Outcomes*** ***n = 1***
Gene ***(11 Participants)***	**Referred to Specialist n = 8**	**Tests Performed n = 7**	**Surveillance n = 5**	**Change in Therapy n = 1**
MYBPC3 n = 3 2 male 1 female	2	(2 participant) Echocardiogram with strain (2) ECG (1) 24h Holter (1) Cardiac MRI (1)	2	0

TNNI3 n = 2 *1 male* 1 female	2	(2 participants) Echocardiogram with strain (2) ECG (2) 24h Holter (1) Cardiac MRI (1)	2	1 Verapamil switched to Metoprolol (1)
MYH7 n = 1 1 female	1	0	0	
MYL3 n = 1 1 female	1			
PKP2 n = 2 1 male 1 female	1	Standard ECG (1) Signal-Averaged ECG (1) Exercise Test (1) Echocardiogram (1) 24h Holter (1) Cardiac MRI (1)	0	
DSC2 n = 1 1 male	1	Standard ECG (1) Exercise Test (1) Echocardiogram (1) 24h Holter (1) Cardiac MRI (1)	0	
DSP n = 1 1 male	1	Standard ECG (1) Signal-Averaged ECG (1) Exercise Test (1) Echocardiogram (1) 24h Holter (1)	0	

Hemochromatosis. Hereditary Hemochromatosis findings were returned to eight participants (3 males, 5 females) who were homozygous for the *HFE* c.845G>A variant and did not previously know their result **(Table 5 and Figure 5)**. Of these, 3 were referred to Department of Gastroenterology and the remaining 5 opted to follow up with their PCP. Of the 3 participants referred to Department of Gastroenterology, 2 underwent iron overload investigations including ferritin level, liver elastography and cardiac MRI. One of these participants also completed additional genetic testing which reconfirmed the finding. Evidence of abnormal iron accumulation was noted in both participants and they were started on therapeutic phlebotomy with periodic surveillance. The third participant was not seen in the Department of Gastroenterology during our study follow-up period. Of the 5 participants who were referred to their PCPs, 1 was found to have abnormal iron profile and was started on therapeutic phlebotomy. Three of the remaining 4 had a normal iron profile and periodic surveillance was initiated in 2 of them. The remaining participant had not been evaluated by their PCP during the study follow-up period.

Table 10. Outcomes in participants with Hereditary Hemochromatosis P/LP variants

	Process Outcomes ***n = 8***			***Clinical Outcomes*** ***n = 4***
Gene ***(8 Participants)***	**Referred to Specialist** **n = 3**	**Tests Performed** **n = 7**	**Surveillance** **n = 3**	**Change in Therapy** **n = 3**

HFE n = 9 3 male 5 female	3	(7 participant) Iron studies (8) Liver MRI (3) Cardiac MRI (1) LFTs (3)	3	Therapeutic Phlebotomy Started (3)

MRI = magnetic resonance imaging; LFTs = liver function tests

Figure-1 Flowsheet for Hemochromatosis

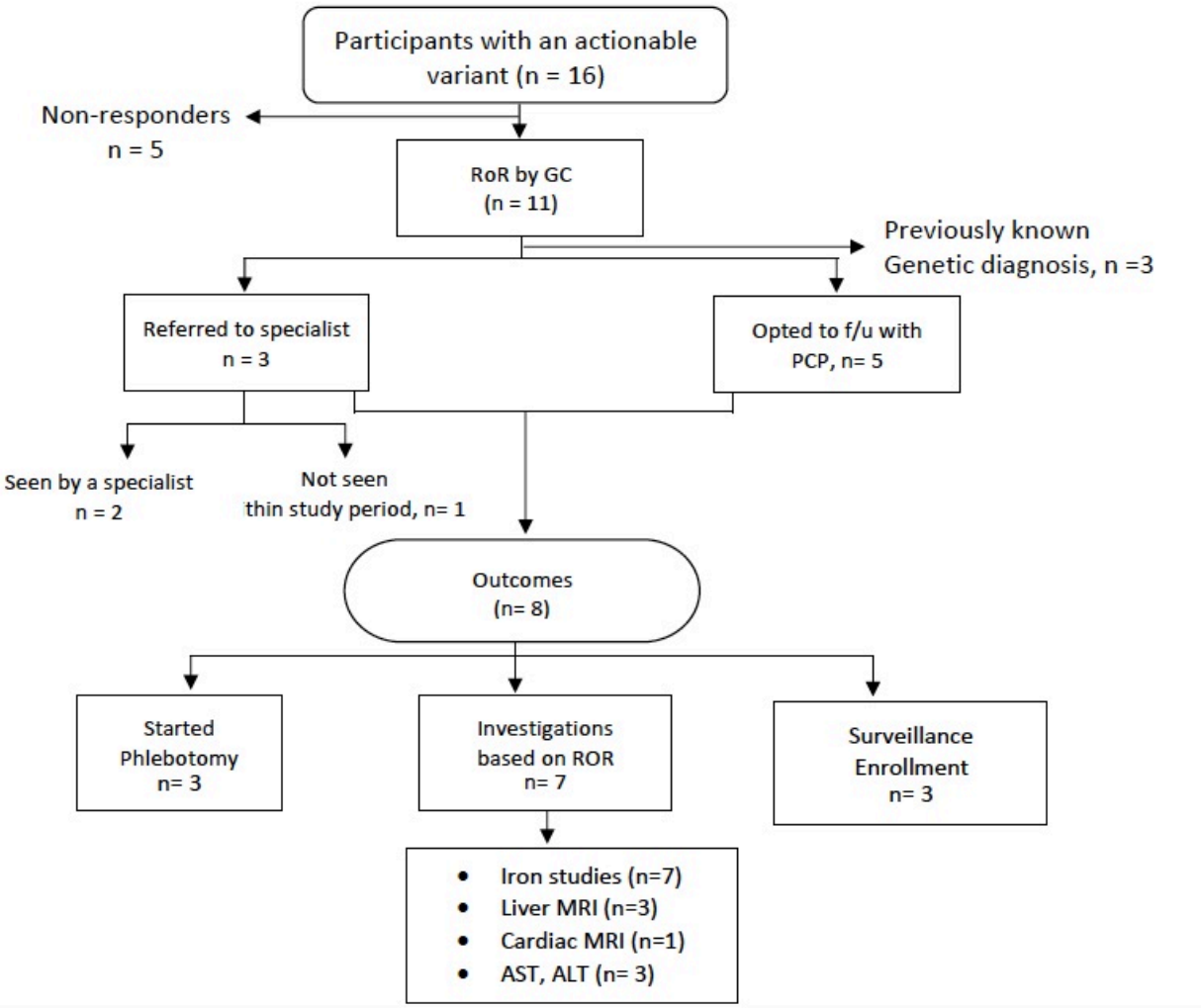

Figure 5. Outcomes in 16 participants with Hereditary Hemochromatosis P/LP variants

RoR= return of results; GC = genetic counselor; f/u = follow up; PCP = primary care provider; MRI = magnetic resonance imaging; AST= aspartate aminotransferase; ALT= alanine transaminase

Factor V Leiden (Homozygous). Of the four participants homozygous for Factor V Leiden *F5* (c.1601G>A), two were referred for further management to their PCP. Neither had a personal history of venous thromboembolism. One participant had a history of deep venous thrombosis and was reviewed by a vascular medicine specialist and subsequently commenced on prophylactic dose rivaroxaban. One participant in addition had an actionable variant in *RET* proto-oncogene and was referred to endocrinology for further management. He had not been seen by endocrinology specialist within the study follow-up period.

Ehlers-Danlos Syndrome, vascular type. A participant in her 60's with a P/LP variant in *COL3A1* (c.4087C>T) was referred to clinical genetics for further assessment. A first degree relative had been diagnosed with spontaneous coronary artery dissection in the 3rd decade of life and was diagnosed with a "connective tissue" disorder but no further details were available. She failed to follow-up within the study follow-up period.

Multiple Endocrine Neoplasia IIA (MENIIA). A participant in their late 60's with a P/LP *RET* (c.2410G>A) proto-oncogene was referred to an endocrinologist and underwent measurement of serum calcitonin, parathyroid hormone, calcium, albumin and vitamin D, as well as 24-hour urine catecholamines and metanephrines, as well as an ultrasound thyroid. These investigations were within normal limits and no further follow-up was planned. A second participant with a P/LP *RET* variant (c.2370G>T) was also homozygous mutation for Factor V Leiden (described above) and referred to an endocrinologist for further management. His lab results came back within normal limits and it was decided that there is no clear benefit of prophylactic thyroidectomy at this time, he was enrolled in annual surveillance.

Familial adenomatous polyposis (FAP). APC P/LP variants were found in two participants who were not previously aware of the result. The first was thought to have a mosaic variant (c.1262G>A) due to a previously normal colonoscopy in their 50's; upper gastrointestinal endoscopy was completed and showed no polyps. This participant was referred to their PCP to coordinate surveillance. The other participant had a variant (c.3920T>A) that does not cause FAP but is a well characterized risk factor for colon cancer especially in individuals with Ashkenazi Jewish background. This participant had an adenomatous colon polyp identified on previous colonoscopy. Surveillance colonoscopy every 5 years was coordinated by her PCP.

Malignant Hyperthermia. A P/LP variant in *RYR2* gene (c.1840C>T) indicating predisposition to malignant hyperthermia was detected in a participant sample. This participant had no anesthesia complications previously. Following RoR, an anesthesia alert was placed in a participant's EHR. She was advised to avoid extreme heat but athletic activity was not restricted.

Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency. A participant homozygous for a P/LP *ACADM* variant (c.997A>G) was referred to clinical genomics for follow-up. In addition, it was recommended that her family members speak with their doctors about testing options to rule out the possibility of having MCAD. This participant had a grandchild who possibly had MCAD. She had not been seen by clinical genomics within the study follow-up period.

Other cancer associated variants. A male participant with a P/LP (*PALB2)* variant (c.172_175delTTGT) was referred to his PCP for screening. A female participant with a P/LP (*PALB2)* variant (c.2748+1G>T) had a previous history of breast cancer (treated with wide local excision and tamoxifen) and was referred to the breast cancer clinic. A mammogram was ordered, and no signs of recurrence or new cancer were observed; she continued to follow-up in the breast cancer clinic. A female with a *CHEK2* P/LP variant (Del Exons 9-10) had a previous history of breast cancer but had her surveillance escalated from a yearly mammogram to a yearly mammogram, bilateral breast MRI and colonoscopy every 5 years. A male with a *CHEK2* P/LP variant (Deletion Exons 1-15) had history of prostate cancer in his 40's and underwent

radical prostatectomy. In addition, he had hyperplastic polyps on previous colonoscopies. Two brothers had prostate cancer in their 50's and a sister died of colon cancer in her 50's. Given his past medical history, he was already followed by specialist and no referral was necessary.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
Outcome data	15*	Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.