Title: Ordering trends and report outcomes for lipid genes on a comprehensive cardiovascular genetics menu

Genetic testing, molecular diagnosis, diagnostic yield, clinical utility, cascade testing

Background/Synopsis – By identifying the molecular etiologies for dyslipidemias, genetic testing can improve diagnostic accuracy, guide personalized medical management recommendations, and identify at-risk family members for proactive surveillance and cascade testing. The utility of genetic testing for dyslipidemias and clinical indications for testing are well described. However, many monogenic dyslipidemias, especially familial hypercholesterolemia, are vastly underdiagnosed.

Objective/Purpose – To assess ordering trends and genetic testing outcomes for dyslipidemia genetic testing performed at a large clinical lab

Methods – We reviewed a retrospective, unselected cohort of individuals undergoing evaluation for personal or family history of dyslipidemia at our laboratory between 2014 and 2020. We classified test orders as (1) single-site genotype analysis (SSA), (2) targeted gene sequencing, next-general sequencing (NGS) panel testing for (3) familial hypercholesterolemia, (4) familial chylomicronemia or (5) sitosterolemia, or a (6) custom NGS panel of up to 167 cardiovascular-related genes chosen by the ordering provider (Table 1). Testing outcomes categorized as positive, uncertain, carrier, or negative were tabulated by test type, gene, and proband age. Statistical analysis was performed using Fisher's exact test.

Results – Overall, 31.42% (n=1046) of probands received a positive finding on genetic testing. Most individuals tested (69.78%) were over the age of 36, although children were significantly more likely to receive positive results ($p<0.00001$). Targeted gene sequencing (51.09%) and SSA (48.95%) had the highest diagnostic rates, suggesting that previous family member diagnosis or strong clinical evidence informed the specific ordering choice. Of all custom NGS panel orders, 36.27% included at least one lipid gene, of which 31.69% also included non-lipid cardiovascular genes suggesting that the patient had non-dyslipidemia cardiovascular features such as cardiomyopathy or arrhythmia. 120 patients had biallelic alterations in *LDLR,* one individual had biallelic alterations in *PCSK9*, and one individual had pathogenic alterations in *LDLR* and *APOB*. Two other individuals had a pathogenic alteration in *LDLR* and were carriers for a second recessive disorder (*LDLRAP1* and *ABCG8*).

Conclusion – Determining a genetic cause for dyslipidemias can provide clinicians with specific guidance for optimizing patient outcomes and follow-up surveillance of at-risk family members. Multigene panel tests may identify compounding molecular diagnostics, which can help in further tailoring treatment. As the field of precision medicine continues to grow, the importance of an accurate molecular diagnosis is increasingly more vital.

Supplemental Materials for Upload

Gene	Testing type				
	Targeted gene sequencing	Familial hypercholesterolemia NGS panel	Familial chylomicronemia NGS Panel	Sitosterolemia	Custom NGS Panel
ABCA1					+/-
ABCG5				+	+/-
ABCG8				+	+/-
APOA1					+/-
APOA5			+		+/-
APOB	+	**+**			+/-
APOC2			+		+/-
APOC3					+/-
APOE					+/-
CYP27A1					+/-
GPIHBP1			+		+/-
LCAT					+/-
LDLR	+	**+**			+/-
LDLRAP1		**+/-**			+/-
LIPA					+/-
LMF1			+		+/-
LPL			+		+/-
PCSK9	+	**+**			+/-
*SLCO1B1**		+/-			+/-

*Testing for SLCO1B1 is targeted CNP testing for c.521T>C associated with statin-induced myopathies

Single site analysis (SSA) would be available for any gene listed above and was offered gratis for at-risk family members following a positive report. +/- denotes that named testing could have included the gene listed; the current offering for FH panel is bolded

Disclosure for all authors:

Full-time, salaried employee of Ambry Genetics, a Konica Minolta Company.