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Scientific Statement

Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association

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Abstract: The genetic basis for more than 2 dozen monogenic dyslipidemias has largely been defined. Genetic technologies, such as DNA sequencing, can detect both rare and common DNA variants underlying dyslipidemias, and these methods are increasingly available. Although patients with extreme abnormalities in low-density lipoprotein cholesterol, triglycerides, or high-density lipoprotein cholesterol may be considered for genetic testing, it is only in a minority of patients that the results will alter treatment or outcomes. Currently, there is potential clinical utility of genetic testing for familial hypercholesterolemia, familial chylomicronemia syndrome, sitosterolemia, lysosomal acid lipase deficiency, and a few other rare disorders, and this will increase the demand for reliable genetic diagnostic methods at lower cost. Clinical indications for genetic testing for most dyslipidemias are not clearly established and currently no guidelines exist. A shared decision-making model between the patient and the provider is essential as patient values and preferences play a very strong role. Potential benefits of genetic testing include providing a firm diagnosis in many cases, guiding optimal management and prevention strategies, advancing care strategies beyond currently available treatments, and contributing to overall scientific progress. Understanding the limitations and risks of genetic testing techniques is also important, as is careful interpretation of genetic test results to achieve the greatest benefit. Here we review laboratory methods, as well as technical, biological, clinical, and ethical implications and applications of genetic testing in dyslipidemias.

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Preamble: The NLA position statement on genetic testing builds on prior NLA recommendations for the patient-centered management of dyslipidemia[1,2] and provides an update to the NLA expert panel statement on familial hypercholesterolemia.[3] The current statement was developed by a diverse panel of experts with expertise in clinical genetics, genetic counseling, clinical lipidology, nursing, and primary care. The process began with the appointment of an Executive Steering Committee by the chair of the NLA Scientific Publications Committee. The Executive Steering Committee then appointed a scientific chair (Robert A. Hegele MD) and vice-chair (Marina Cuchel MD PhD) and then selected expert panel members. The chair and expert panel members then developed a set of key clinical questions to be addressed and writing assignments were determined based on expertise. When possible, recommendations were made after grading the quality and strength of the scientific evidence. Final recommendations required a majority consensus of the expert panel. The NLA expert panel graded the recommendations using the American College of Cardiology/American Heart Association Evidence-Based Grading System (Supplemental Table 1).[4] In rating the class (or strength) of the recommendation, consideration was given to the "net benefit" after taking into account potential benefits and risks or harms associated with the test or intervention. For rating the level (or quality) of the evidence, consideration was given to obtaining the highest quality evidence to support a recommendation.

I. Introduction—monogenic and polygenic lipid disorders

Genetic testing is increasingly becoming a common consideration in the clinical care of patients with dyslipidemia. Dyslipidemias for which genetic testing could be clinically useful include familial hypercholesterolemia (FH), familial chylomicronemia syndrome (FCS), sitosterolemia, lysosomal acid lipase deficiency, and other disorders. However, clinical indications for genetic testing for most dyslipidemias are not clearly established. Furthermore, no clinical practice guidelines currently exist for genetic testing in patients with possible hereditary dyslipidemia. Here we review issues related to genetic testing in dyslipidemia using a "frequently asked questions" format, with display items and a glossary of terms, to provide clinical guidance to health care providers.

a) What is the difference between a monogenic and polygenic dyslipidemia?

Circulating levels of lipids and lipoproteins are determined by environmental and heritable factors.[5] Genetic causes of dyslipidemias include both rare DNA variants with a large phenotypic impact and common DNA variants with individually small effects.[6]

Monogenic dyslipidemias are caused by rare large-effect variants, and their inheritance follows Mendelian rules.[7] Confirming a diagnosis of monogenic dyslipidemia using genetic testing can affect management and screening to identify affected family members, termed "cascade screening", for example, as has been well defined in FH.[8,9]

In contrast, polygenic dyslipidemias result from concurrent contributions of multiple common variants, that is, single nucleotide polymorphisms (SNPs, see glossary), whose aggregate effect on lipoprotein levels can resemble a large-effect rare variant.[10,11] Inheritance does not follow Mendelian rules. The impact of such common variants is quantified using a polygenic score.[12] First-generation polygenic scores comprised a limited number of variants for multiple forms of dyslipidemia.[13–17] More recently, polygenic scores constructed from millions of SNPs with vanishingly small individual effect sizes are informative for common diseases, such as coronary artery disease; they include not only SNPs that affect lipoprotein levels, but also those affecting other pathways and risk factors. Future analogous large scores may become useful for assessing dyslipidemias. Although polygenic scores are important in the genetic underpinning of dyslipidemia and may someday play a role in risk stratification, more work is needed to determine their appropriate application in clinical practice. In addition, validation studies are needed to verify the accuracy of specific genetic testing platforms and polygenic score algorithms.

Key points

- Rare, large-effect DNA variants (mutations) cause monogenic or Mendelian dyslipidemias; genetic testing for such variants may have clinical utility.
- Common small-effect DNA variants (SNPs) in aggregate create susceptibility to dyslipidemia or common diseases. This susceptibility is quantifiable in a polygenic score, whose clinical utility is currently less clear.

b) What are the important clinical features that characterize select inherited lipid disorders?

The molecular genetic basis is well established for 25 monogenic dyslipidemias that are characterized by extreme blood levels of low-density lipoprotein cholesterol (LDL-C), triglycerides, high-density lipoprotein cholesterol (HDL-C), and/or other lipids.[7] The biochemical disturbance is the primary element needed for diagnosis and classification, but several conditions are associated with syndromic findings, shown in Table 1. Pathognomonic clinical features are variably present even when there is a definite DNA lesion; when present they can facilitate diagnosis and trigger the consideration of genetic testing. Some systemic complications require subspecialist assessment and follow-up.

The prototypical condition for which genetic testing is ordered is FH, a common codominant disorder. The

Table 1 Clinical features of selected monogenic dyslipidemias

Archetypal monogenic disease or syndrome	FH	FCS	FDBL	LCATD	ABL, FHBL
Primary severe lipid disturbance	↑ LDL-C	↑ TG	↑ TG and ↑ TC	↓ HDL-C	↓ LDL-C
General					
Failure to thrive	−	++	−	−	++
Cardiovascular system					
Early atherosclerosis	++	+/−	++	+/−	−
Coronary: angina, ACS, MI	++	+/−	++	+/−	−
Cerebrovascular: TIA, amaurosis fugax, stroke	+	+/−	+	+/−	−
Peripheral vascular: claudication	+	+/−	++	+/−	−
Arterial bruits	+	−	+	−	−
Aortic valve disease	+	−	−	−	−
Eyes					
Xanthelasma	++	−	+	−	−
Arcus cornealis	++	−	−	−	−
Lipemia retinalis	−	++	−	−	−
Corneal opacities	−	−	−	++	−
Atypical retinitis pigmentosa	−	−	−	−	++
Gastrointestinal system					
Abdominal pain, nausea, vomiting	−	++	−	−	−
Hepatosplenomegaly, hepatosteatosis	−	++	−	−	+
Pancreatitis	−	++	−	−	−
Fat malabsorption	−	−	−	−	++
Renal					
Proteinuria	−	−	−	+	−
Renal insufficiency	−	−	−	+	−
Blood					
Erythrocyte abnormalities					
Target cells	−	−	−	++	−
Acanthocytes	−	−	−	−	++
Mild anemia	−	−	−	+	+
Neurological					
Peripheral neuropathy	−	−	−	++	++
Ataxia	−	−	−	−	++
Posterior column signs	−	−	−	−	++
Xanthomas					
Extensor tendon	++	−	−	−	−
Tuberous	+/−	−	++	−	−
Plantar	+/−	−	++	−	−
Palmar	+/−	−	++	−	−
Periosteal	+	−	−	−	−
Peripatellar	+	−	−	−	−
Intracranial	+	−	−	−	−
Eruptive	−	++	−	−	−
Digital web spaces	+/−	−	−	+	−

ABL, abetalipoproteinemia; ACS, acute coronary syndrome; FCS, familial chylomicronemia or monogenic chylomicronemia; FDBL, familial dysbetalipoproteinemia; LCATD, lecithin cholesterol ester transferase deficiency; FH, familial hypercholesterolemia; FHBL, familial hypobetalipoproteinemia; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; TC, total; cholesterol; TG, triglyceride; TIA, transient ischemic attack; Key.

++ feature is strongly and consistently present in individuals with the dyslipidemia; + feature is characteristic of the dyslipidemia, but is not consistently seen in individuals with the dyslipidemia.

+/− feature is sometimes seen in individuals with the dyslipidemia, but is not considered to be characteristic of the syndrome.

− feature is not part of the clinical presentation of the dyslipidemia.

heterozygous form has a population prevalence of approximately 1 in 250.[18,19] Patients with FH can display characteristic clinical features (see Table 1), including premature plaque development in the coronary, central, and peripheral vasculature, leading to early-onset atherosclerotic cardiovascular disease (ASCVD) events, including myocardial infarction, stroke, and limb ischemia.[8,9,19] As early diagnosis and initiation of lipid lowering treatment are associated with a significant reduction of risk to develop ASCVD,[20] genetic testing is a useful tool to implement cascade screening.

Another common dyslipidemia is hypertriglyceridemia, which if severe can lead to life-threatening acute pancreatitis.[21] Clinical features of the most severe forms include eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, and increased risk of acute pancreatitis. Genetic analysis may be helpful in certain cases of severe hypertriglyceridemia, such as monogenic chylomicronemia, which is also called FCS.[22,23] Among patients with severe hypertriglyceridemia, polygenic causes are 50- to 100-fold more common than monogenic causes.[17]

Other dyslipidemias include the following: 1) familial dysbetalipoproteinemia, formerly type 3 hyperlipoproteinemia, which is characterized by roughly equimolar elevations of total cholesterol and triglycerides and by tuberoeruptive and palmar xanthomas[24]; 2) low HDL-C states, such as Tangier disease and familial lecithin cholesterol acyl transferase (LCAT) deficiency, which can present with corneal findings, neuropathy, and renal involvement[25]; and 3) low LDL-C states, such as abetalipoproteinemia and homozygous familial hypobetalipoproteinemia, which have multisystem involvement that can be averted by early diagnosis and treatment with high dose fat soluble vitamins, particularly vitamins A and E.[26]

Key points

- Of 25 monogenic dyslipidemias, the most common is FH.
- Monogenic dyslipidemias have characteristic clinical features that are variably present. These features, if present, can be useful in guiding genetic testing.
- In FH, a codominant disorder, genetic testing may be used for the early identification of affected family members through cascade screening.

c) If a patient has phenotypic presentation of a genetic lipid disorder, when should genetic testing be considered?

Genetic testing could be considered in several scenarios (Table 2). First, genetic results may be directly relevant to the diagnosis, treatment, and prognosis of the patients and their family members. For example, a genetic diagnosis of FH may have a positive public health impact[9] and may also confirm a clinical diagnosis and prompt cascade screening. Cascade testing of relatives of people with FH has been given the tier 1 classification by the US Centers for Disease Control and Prevention Office of Public Health Genomics. Genetic diagnosis of FCS,[22] sitosterolemia[27], or cerebrotendinous xanthomatosis (CTX)[28] similarly may have direct implications for patient care (Table 3). Second, genetic results may provide information for the management of patients and family members, even in the absence of high grade evidence that treatment and outcomes can be affected. For instance, homozygotes for *ABCA1* loss of function variants can have increased risk of diabetes, neuropathy, and possibly ASCVD.[29] Management includes monitoring for complications and ASCVD prevention, even though the benefit has not been definitively proven. In addition, patients with only mild hypercholesterolemia whose family members have molecularly confirmed FH might be more likely to adhere to statin therapy. Finally, genetic results may not affect management but still have academic value, with potential to increase our understanding and also to identify possible novel therapeutic approaches.[23]

Table 2 Potential indications for genetic testing in dyslipidemias

- Strong clinical suspicion of a genetic dyslipidemia.
- Strong family history of dyslipidemia or its complications.
- Presence of related syndromic features (see Table 1).
- Evidence that testing might change management.
- Available and effective early interventions exist.
- Eligibility for new or investigational drugs.
- Patient preference.
- Family planning.

Key points

- There are several examples of monogenic dyslipidemias in which the molecular diagnosis can affect clinical decision making and patient care.
- A positive genetic test can direct cascade screening of family members to identify additional cases.

II. Genetic testing

a) What are the types of genetic testing now available for dyslipidemia?

Genetic testing[23] includes the following methods: 1) genotype only previously described DNA variants (eg, DNA microarrays or TaqMan genotyping) and/or 2) scan all DNA nucleotide positions within a single gene, a panel of selected genes, or exome of genome (see glossary), enabling detection of both previously known and newly discovered DNA variants (eg, Sanger or capillary electrophoresis sequencing, targeted next-generation gene sequencing panels, exome sequencing [ES], or genome sequencing [GS]).[23]

Some targeted sequencing panels for dyslipidemia have been clinically validated[30,31] and are the current gold standard for diagnosis in dyslipidemias,[32] for example, targeted panels for FH genes, or "pandyslipidemia" panels for all monogenic dyslipidemias.[7,30] The same result from a targeted panel can be achieved by performing ES or GS analysis and then masking most results, reporting only findings from genes of interest.

Table 3 Clinical impact of genetic diagnosis in selected monogenic dyslipidemias

Condition	Causative gene(s)	Management effect
Familial hypercholesterolemia	*LDLR, APOB, PCSK9* heterozygous FH: single pathogenic variants; homozygous FH: biallelic pathogenic variants in the above and *LDLRAP1*	Cascade screening May influence insurance eligibility for inhibitors of PCSK9 eg, evolocumab (Repatha) or alirocumab (Praluent) or lomitapide (Juxtapid—inhibitor of microsomal triglyceride transfer protein) Treatment selection: eg, in homozygous FH, a genetic diagnosis may support the need for apheresis; also in homozygous FH having at least one LDL receptor allele with retained function predicts response to PCSK9 inhibition.
Familial chylomicronemia	*LPL, APOC2, APOA5, LMF1, GPIHBP1* biallelic pathogenic variants	Volanesorsen (Waylivra—antisense inhibitor of apolipoprotein C-III) available in Europe.
Sitosterolemia	*ABCG5/ABCG8* biallelic pathogenic variants	Reduced dietary sterol intake plus ezetimibe to prevent ASCVD
Cerebrotendinous xanthomatosis	*CYP27A1* biallelic pathogenic variants	Chenodeoxycholic acid to prevent multiple progressive neurological symptoms.
Cholesterol ester storage disease (Wolman syndrome; lysosomal acid lipase deficiency)	*LIPA* biallelic pathogenic variants	Sebelipase alfa therapy (Kanuma—intravenous enzyme replacement for lysosomal acid lipase).
Abetalipoproteinemia or homozygous familial hypobetalipoproteinemia	*MTTP* or *APOB* biallelic pathogenic variants, respectively	Can help confirm a clinical diagnosis and provides justification for lifelong reduction in dietary fat intake plus high dose fat soluble vitamins.

Key points

- Dedicated genotyping methods yield a few possible results limited to genetic variants that have already been reported.
- Sequencing panels targeted to known dyslipidemia genes provide comprehensive results and are more commonly used than ES or GS.

b) How is genetic testing performed?

Genetic testing laboratories typically accept various sample types, including whole blood, saliva, or buccal swabs. For inherited dyslipidemias, analysis usually involves DNA sequencing. Additional analysis, including evaluation for deletions and duplications (del-dups), may be included, depending on the condition.[33–35] For instance, ~10% of causative variants in FH are del-dups or large copy number variants,[36] which can be missed by certain DNA sequencing methods, so genetic testing must be able to evaluate for these. Variants are classified based on the American College of Medical Genetics (ACMG) guidelines.[37]

Although ordering the genetic test itself is usually straightforward, the results and their implications are often complex. Therefore, before ordering genetic testing, the clinician should discuss the implications of genetic testing with the patient and obtain informed consent. In some cases, genetic counseling may be indicated before ordering testing. In addition, once results are released to the ordering clinician, they should be reviewed with patients via posttest genetic counseling.[33]

Key points

- It is important to educate the patient and to obtain informed consent before performing genetic testing.
- Methodologies typically include at least DNA sequencing.
- The clinician should assess the necessity of additional analyses, such as the evaluation of del-dups and copy number variants.
- Patients should receive genetic counseling to discuss the implications of the results, in many cases before ordering genetic testing.

c) How accurate are genetic test results?

Accuracy of genetic test results requires consideration of both analytic and clinical validity. The Centers for Medicare and Medicaid Services regulates the analytical validity of clinical genetic tests by requiring clinical laboratories to obtain certification under the Clinical Laboratory Improvement Amendments of 1998 (CLIA). However, research and direct-to-consumer (DTC) laboratories are not required to obtain CLIA certification.[38] This can result in false positive or negative results.[39] Criteria for clinical validity of genetic diagnostic tests are not fully established, and testing is not currently regulated. Therefore, it is important for clinicians to assess clinical validity before using the results to guide management.

Key points

- Not all genetic tests are created equal. Not all laboratories will yield the same genetic testing results. It is important for clinicians to review analytic and clinical validity of a test before using the result for medical management decisions.
- DTC genetic testing may provide inaccurate data with both false positive and false negative results; positive results returned from a DTC company should be confirmed using a clinical genetic testing laboratory.

d) Are polygenic risk scores for hypercholesterolemia available?

At least 15 different polygenic scores for LDL-C levels have been reported in research studies.[6,12] However, none of them is the accepted "gold standard" score for routine clinical use. Each score combines different LDL-C–raising SNPs from throughout the genome that have been reliably shown in genome wide association studies to have modest but reproducible effects on LDL-C levels. In research studies, various scores demonstrate the same thing, that is, 20 to 30% of patients with very high LDL-C levels have a high polygenic score rather than a single gene mutation driving the high LDL-C levels.[15] These patients will sometimes have affected family members and might still benefit from biochemical cascade screening. However, for the FH phenotype, there is currently no consensus on how to use polygenic scores or the best score to use. In instances when the genotype and phenotype may not agree, clinical decisions should be guided by the biochemical LDL-C phenotype.

Key points

- Up to 30% of patients clinically suspected to have monogenic FH actually have polygenic hypercholesterolemia.
- Management should be based on the severity of LDL-C elevation rather than whether the patient has monogenic or polygenic etiology; the clinical utility of polygenic scores is presently unclear.
- Implications of polygenic hypercholesterolemia for cascade family screening for FH among relatives need to be defined.

e) Where can I order a genetic test for dyslipidemia?

Once the decision has been made to proceed with genetic testing, with the patient's consent, we advise using a CLIA-certified laboratory that offers the appropriate gene panel for the patient's likely diagnosis. A noncomprehensive list of some commercial laboratories that provide this type of service is shown in Supplemental Table 2. The National Institutes of Health also posts a registry of genetic testing services and identifies those that report they are CLIA certified (see https://www.ncbi.nlm.nih.gov/gtr/). Many commercial laboratories may offer family screening for additional members at a reduced price within a certain timeframe; it is important to consult with the genetic counselor before proceeding with this type of screening.

III. Would my patient benefit from a genetic test?/deciding to order a genetic test

a) How does the result of a genetic test influence treatment?

The potential impact of genetic testing results on treatment depends on the disorder and patient preferences and circumstances. Positive genetic confirmation of FH may improve adherence with LDL-C–lowering treatment, may permit access to certain treatments (see Table 3), and may motivate cascade screening of family members.[20] Patients with a positive DNA result may also feel more motivated to undergo screening for subclinical or clinical ASCVD. For other patients who are already very committed to treatment, genetic testing may have no further impact on their adherence or further clinical screening, but may still have an impact on the uptake of cascade testing. If no causative mutation is identified, some patients might experience the potential negative impact of decreased compliance and reduced motivation, possibly resulting in some patients discontinuing treatment.

Key points

- Positive genetic test results may increase patient compliance and motivation.
- Negative genetic test results may have the opposite effect in some patients.
- Genetic testing may facilitate targeted treatment for specific disorders (see Table 3).

b) Are there current examples of clinically actionable genetic test results for dyslipidemias?

There are several genetic tests in which the results lead to clinical actions for dyslipidemias (Table 3). For instance, a genetic diagnosis of FH may prompt cascade screening, escalation of preventive measures for ASCVD, screening for subclinical ASCVD, and facilitating access to proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors in some jurisdictions. A genetic diagnosis of FCS allows access to volanesorsen treatment in Europe. A genetic diagnosis of sitosterolemia changes treatment focus from statins (which have attenuated efficacy in sitosterolemia) and possibly from lipoprotein apheresis to reduced dietary sterol intake (and discontinuation of over-the-counter phytosterol dietary supplements) plus ezetimibe to prevent ASCVD. Genetic diagnosis of CTX may facilitate early initiation of lifelong chenodeoxycholic acid to prevent debilitating complications. A genetic diagnosis of cholesteryl ester storage disease (CESD or Wolman disease or lysosomal acid lipase deficiency) may expedite third party coverage for treatment with sebelipase (intravenous lysosomal acid lipase infusion) to prevent cirrhosis. Finally, in both abetalipoproteinemia and homozygous hypobetalipoproteinemia, a positive DNA diagnosis can confirm a clinical diagnosis, which can have an impact on advice for lifelong diet and vitamin intake.

c) Does genetic testing in familial hypercholesterolemia alter risk stratification, change outcomes, and affect treatment choices?

Genetic testing in FH can predict clinical outcomes. For instance, among individuals with elevated LDL-C (ie, ≥190 mg/dL, with or without a clinical diagnosis of FH), having a heterozygous pathogenic FH-causing mutation is associated with a 22-fold increased risk of ASCVD compared with a normolipidemic individual, whereas among individuals with elevated LDL-C but no FH-causing mutation, the risk is 6-fold increased.[40] In addition, among individuals with clinically diagnosed heterozygous FH, the presence of a monogenic FH-causing mutation was associated with doubling of ASCVD risk compared with individuals who had either a polygenic cause or no identified genetic cause.[41] Furthermore, individuals with both a monogenic causative variant plus high polygenic score had 3-fold increased risk of ASCVD compared with individuals with clinically diagnosed FH with no identifiable genetic cause.[41] However, individuals with elevated LDL-C or clinically suspected FH are all at very high risk of ASCVD (between 6- and 22-fold), irrespective of the precise genetic etiology; management should be based on their LDL-C elevation and not their genotype.[42,43] Finally, in patients with homozygous FH, genetic results may predict LDL-C lowering response to PCSK9 inhibitor therapy, which is absent in the setting of receptor-null mutations, somewhat better in the presence of receptor-defective mutations, and may be best in the presence of a gain-of-function mutation in the PCSK9 gene.[44] In addition, identification of homozygous or compound heterozygous mutations in the *LDLR* gene may guide gene therapy in the future.

Key points

- Patients with severe primary hypercholesterolemia, and suspected to have FH, are at high risk of ASCVD; the precise genotype is not predictive in an individual patient.
- Intensity of treatment should be guided by LDL-C elevation rather than the underlying genotype.
- Prospective studies are needed to determine whether genetic testing for FH in addition to routine lipid profile testing will alter cardiovascular outcomes by identifying the appropriate LDL-C–lowering therapy based on a patient's gene mutations.

d) Does genetic testing in severe hypertriglyceridemia improve diagnosis and treatment choices?

Most patients with severe hypertriglyceridemia (triglyceride $\geq$ 1000 mg/dL or $\geq$11.1 mmol/L) have multifactorial or polygenic chylomicronemia; monogenic chylomicronemia (ie, FCS) is seen in only 1 to 2% of such patients.[17] There is no such condition as autosomal dominant hypertriglyceridemia. FCS is suggested by the absence of secondary factors, ascertainment at a young age, low levels of apolipoprotein (apo) B, and high lifetime risk of acute pancreatitis.[21,22] Irrespective of genetic etiology, therapy centers on a very low-fat diet, limiting refined carbohydrate foods and limiting or completely abstaining from alcohol; drugs such as fibrates, niacin, or high doses of omega-3 fatty acids are somewhat more efficacious in polygenic/multifactorial vs monogenic chylomicronemia.[21,45] Investigational treatments, such as biologic agents that reduce apo C-III (eg, volanesorsen) or angiopoietin like protein 3 (ANGPTL3) (eg, evinacumab), reduce triglyceride drastically.[46] The precise genetic basis in severe hypertriglyceridemia may prove to be helpful in guiding therapy. Family members of a patient with severe hypertriglyceridemia are more likely to also have hypertriglyceridemia, although the trait does not follow an obvious genetic pattern; family members should be screened biochemically.

Key points

- Severe hypertriglyceridemia in adults is usually polygenic or multifactorial, often involving a strong environmental component.
- In the European Union, volanesorsen is approved only for patients with genetically confirmed FCS.
- In determining treatment, the degree of hypertriglyceridemia is usually more important than knowing the precise genotype.
- Screening of family members for severe hypertriglyceridemia is important irrespective of the genetic basis.

e) Does genetic testing in low HDL-C syndromes alter treatment choice?

Currently, no therapy has been found to improve outcomes in patients with low HDL-C. Targeted therapies for specific rare monogenic forms of depressed HDL-C are under investigation, including infusion of recombinant human LCAT,[47] or infusion of reconstituted apo A-I.[48] At present, management of patients with low HDL-C should focus on existing proven therapies that reduce ASCVD risk in general, including statins[49] and, if familial LCAT deficiency is suspected (see Table 1), on optimizing management of renal disease.

Key points

- There is no evidence that genetic testing in low HDL-C syndromes will guide interventions that will reduce ASCVD outcomes.

f) What are the risks of genetic testing?

Potential risks of genetic testing include both psychological and financial consequences. Genetic testing can produce a range of emotions, including anxiety, depression, or guilt. It can also affect family dynamics as the results often have implications beyond the individual who underwent testing, including identifying nonpaternity.[50] In addition, genetic discrimination is an important risk. To protect against this, the Genetic Information Nondiscrimination Act (GINA) was passed into US federal law in 2008. GINA protects against health insurance companies or employers from using genetic information to make decisions regarding insurance coverage and eligibility or employment. However, it does not apply to long-term disability or life insurance. Life insurance companies can use genetic test results to determine eligibility, rates, and other policies. Consequently, some individuals will obtain life insurance before undergoing testing. GINA does not apply to all groups; exclusions include people in the military or those who work at a company with $<$15 employees.[51]

Key points

- Consultation with a genetic counselor is recommended before and after the testing.
- Before genetic testing, benefits and risks should be reviewed with the patient.
- GINA protects most individuals from genetic discrimination by their employers and/or their health insurance company, but does not apply to life insurance or long-term disability insurance.

g) What is the cost of genetic testing?

The cost of genetic testing has significantly decreased since 2010, making access feasible for many patients.[52] The cost depends on a various factors, including the complexity of the analysis and interpretation, with targeted testing for a known familial variant being typically less expensive than the initial test to identify the genetic variant in the proband.[53] Approximate costs per sample are $300 to 600, $800 to 1200, and $1500 to 5000 for a targeted sequencing panel, ES, and GS, respectively.[23] Insurance coverage varies widely depending on the condition and type of testing ordered. The cost billed to insurance providers can differ from the direct cost to patients; many laboratories reduce costs for out-of-pocket payments.

Key points

- Declining costs and increasing clinical utility will make genetic testing feasible in selected patients with dyslipidemia and/or their asymptomatic relatives.
- The cost of targeted genetic testing for family members is typically less than the cost for probands.

IV. Laboratory test reporting

a) How does the laboratory report results of a genetic test?

Results are usually reported on forms such as that shown in Figure 1. Although there are no universal standards, report forms generally include the following: 1) patient identifier, demographic and clinical information, including reason for the test or pretest diagnosis; 2) description of the gene panel content or list of genes tested; 3) test performance metrics; 4) main result overview or summary, including positive or negative result notification; 5) interpretation of variants using established criteria, such as those from the ACMG, subdividing pathogenic and likely pathogenic variants vs variants of uncertain significance (VUSs) and likely benign variants; 6) additional information, such as any research publications related to detected variants; 7) sometimes a more complete, detailed table of variants found in the patient's sample; 8) results of polygenic testing for dyslipidemia if performed plus interpretation; 9) reports of any secondary or incidental findings, if requested and consent is provided; 10) recommendations; and 11) statement of limitations, disclaimers, and caveats. Some reports contain only a subset of these items. In addition, because knowledge is rapidly advancing, some laboratories monitor and review variants periodically and can reclassify them based on new research.

b) If the laboratory reports a DNA variant in a dyslipidemia gene in my patient, how do I know it is pathogenic?

Key points

- There are several elements required for a credible genetic test report.
- Attributing pathogenicity to a particular variant can differ between laboratories; there are no universally applied standards.

Even when the laboratory finds a rare variant in a known causative gene for monogenic dyslipidemia, its causality or pathogenicity is not guaranteed. DNA changes in the coding sequence may be synonymous or nonsynonymous at the protein level (see glossary) but the functional or pathogenic impact cannot be directly predicted.[37] The highest grade of evidence for pathogenicity is provided by a functional study performed in a research laboratory showing that the mutation causes a measurable change in an assay or model system. Familial segregation analysis proving genotype-phenotype concordance across generations is also helpful; that is, affected family members carry the variant, whereas unaffected members do not. Very rare coding variants in target genes are potentially more likely to be pathogenic. Conversely, the presence of the variant in healthy, disease-free individuals argues against pathogenicity, but does not guarantee it because of reduced penetrance, whereby carriers of certain variants do not express the clinical phenotype.[54]

Additional evidence for pathogenicity comes from 'bioinformatics', that is, computational modeling and analysis. This involves use of prediction software tools that use complex algorithms to predict the impact of the amino acid change based on evolutionary conservation, predicted 3-dimensional structure of the protein, and other data.[55] However, these methods sometimes give inconsistent results for the same variant; many laboratories use in-house algorithms and refer to annotations from different public and private disease databases. Rarely, a research scientist will have performed laboratory experiments proving that a particular variant functions improperly and can therefore explain the abnormal clinical phenotype. When there is an insufficient body of evidence to support or exclude a pathogenic role, the term "variant of unknown (or uncertain) significance" is used. Even after manual adjudication by expert geneticists, there can be disagreement regarding potential pathogenicity. Nonetheless, trained, knowledgeable, and skilled individuals must be available to interpret genetic tests.[56]

c) How do I handle incidental findings on the genetic report?

Researchers are familiar with unexpected off-target "incidental findings" in ES or GS, that is, findings unrelated to the disorder under consideration.[57] Because such findings arise frequently, a policy regarding communication

LipidTech Genetic Testing report

Patient details

Name: Gregory Mendel*
Date of birth: 29 Feb 1988
Gender: Not specified
Patient ID: GATATC-12
Sample received: 20 Jan 2020
Report date: 15 Feb 2020

Center details

Requested by: Dr. Frank Crick*
Address: 1 Double Helix Road, Arkadelphia, AR 71923

Result of the genetic analysis

Heterozygous pathogenic variant in the *LDLR* gene.

Result summary

Gene: *LDLR* (RefSeq NM_000527.4)
Genetic identifier: c.1646G>A (exon 11)
Protein identifier: p.Gly528Asp (HGVS Nomenclature p.Gly549Asp)
Mutation class: Amino acid change

Interpretation

This mutation is directly associated with familial hypercholesterolemia, since its pathogenicity has been validated. Validation study: Hobbs et al. (1990) *Ann Rev Genet* 24:133

Recommendations

Referral to a genetic counsellor is recommended.

Methods

LipidTech's FH genetic analysis detects substitutions and indels in exons and intron-exon boundaries of the following genes:

LDLR gene (familial hypercholesterolemia): 18 exons
PCSK9 gene (ADH3): 12 exons
LDLRAP1 gene (ARH): 9 exons
APOB gene (familial defective APOB): regions of exons 26 and 29 involved in LDLR binding
APOE gene: region of exon 4

The assay also detects copy number variations (CNV) in the *LDLR* gene associated with FH.

Proprietary algorithms are used to detect genomic deletions and duplications (del-dups) in all 18 exons and the promoter region in the *LDLR* gene.

All genes are fully analyzed by next generation sequencing on the Illumina MiSeq sequencer. 70 regions of interest are amplified from genomic DNA, isolated from whole blood or saliva, in multiplex PCR reactions that include highly purified primers for the specific amplification of regions in which mutations causing FH can be found.

Figure 1 Sample genetic test report form. Technical terms are explained in section IV and the glossary.

to patients is required. For example, if ES in a patient with dyslipidemia incidentally identifies a mutation in the familial breast cancer *BRCA1* gene, what is the obligation to report it? Furthermore, hundreds to thousands of incidental VUSs in many genes may be identified with both ES and GS. What is the most appropriate way to evaluate and communicate these findings? A conflict of interest might arise between the researcher's or clinician's "duty to inform" at-risk patients and family members and the individual's "right not to know".[58] Furthermore, genetic testing could infringe on family privacy because results indirectly provide information about family members[59] and may include mispaternity. These possibilities should be discussed with the patient before testing.

Key points

- Factors that increase the likelihood that a DNA variant is pathogenic include the following: 1) rarity in or absence from the general normolipidemic population; 2) cosegregation with disease in families; 3) computer models predict a deleterious mechanistic impact; and 4) a research scientist has performed experiments to show that the mutation has deleterious effects (eg, in a petri dish or an animal model).
- If there are not enough data to support or exclude the pathogenicity of a given variant, it is labeled as "variant of unknown (or uncertain) significance" or VUS.

The ACMG recommends that incidental findings for about 60 genes should be communicated to patients,[60], which are listed at https://www.ncbi.nlm.nih.gov/clinvar/docs/acmg/. One way to minimize the chance of detecting incidental findings is to use a targeted disease panel, which only tests a limited number of genes instead of the complete exome or genome. If ES or GS is planned, the possibility of detecting incidental or secondary findings should be discussed with the patient in advance, with informed consent and various options for reporting provided to account for the possible range of results.

In a familial case related to a confirmed carrier of a specific identified pathogenic variant, Sanger capillary electrophoresis sequencing is used for point mutation detection or multiplex ligation-dependent probe amplification (MLPA) analysis is used for detection of CNVs.

Genetic variant reporting

DNA variants are identified and classified by comparison with reference sequence against the ClinVar database. If a variant is identified, the report will specify the mutation found: the gene, exon, nucleotide, and amino acid position; and pathogenicity status (pathogenic, probably pathogenic, or possibly pathogenic). The report will also indicate whether the specific mutation is homozygous or heterozygous.

Heterozygous pathogenic, possibly pathogenic or probably pathogenic mutations found in *LDLRAP1* will be reported to inform about carrier status of the patient.

Common polymorphisms or SNPs are considered as having no effect on protein levels or activity and are not reported.

Silent variations or intronic variations for which no changes in the splicing patterns have been found with bioinformatic analysis are classified into a non-pathogenic group and are not reported. In these cases, the result of the analysis will appear as "No Pathogenic Mutations Detected" in the report.

All variants (SNPs and not reported variants) for all samples are available upon request.

Limitations

Since *PCSK9* exons 6 and 9, as well as *APOB* exon 29, contain sequences that can interfere with DNA amplification, LipidTech cannot ensure the correct identification of variants in these amplicons.

For cases with "no mutations detected" there is still a chance that the patient carries a causative variant in genes that were not analyzed.

*names are fictitious

Figure 1 (*continued*).

Key points

- The possibility of detecting incidental findings unrelated to the main condition under consideration is reduced by using a targeted gene panel.
- If more comprehensive ES or GS is used, there should be discussion in advance with the patient regarding the possible detection of incidental findings that could have health and family consequences outside the sphere of dyslipidemia.
- Incidental findings for about 60 genes unrelated to lipids should be communicated to patients

d) How reliable are genetic results for dyslipidemia from direct-to-consumer companies such as 23andMe?

In general, genetic testing through DTC companies, such as 23andMe is not recommended for medical management decisions as there are multiple inherent limitations with these tests. 23andMe now reports results for a very limited number of FH mutations. DTC companies are not required to meet CLIA analytical validity standards and may have higher false positive and negative genetic test results compared with clinical laboratories.[38] In addition, these DTC tests typically only focus on finding a few familiar or relatively common mutations associated with a certain condition. Thus, if a patient has a negative result from a DTC laboratory, a more complete test from a clinical laboratory may have the possibility to identify patients who have a truly pathogenic variant using a comprehensive genetic test.

Many companies provide consumers with access to their raw data in addition to the official report. These raw data can be provided to a third-party company for analysis. Such analyses have very high false positive rates (up to 40%), related in part to errors in sequencing, and consequently, any variant identified in the raw data should be clinically confirmed.[39]

Key points

- Genetic testing through a DTC company is not comprehensive and results often require confirmation in a clinical laboratory.
- Negative genetic test results from DTC companies may not necessarily rule out the presence of a genetic dyslipidemia.

V. Counseling patients and families

a) What should be included in genetic counseling for patients considering genetic testing for lipid disorders, including FH?

Genetic counseling for patients with dyslipidemias should be provided by a qualified clinician, such as a genetic counselor. Genetic counseling should include collection of at least a 3 generation family medical history (pedigree), risk assessment incorporating personal and family medical histories, discussion of probable mode of inheritance and recurrence risk to relatives, anticipatory guidance regarding possible genetic testing results (positive, negative, indeterminant, VUS), and, if an individual is interested in pursuing genetic testing, discussion of the benefits, risks, and limitations.[61,62] Genetic counseling should also include a plan for communicating information to at-risk relatives to facilitate cascade testing, discussion of applicable reproductive options, provision of patient-centered resources (ie, information from patient advocacy organizations, such as the FH Foundation), and psychological assessment of patient well-being, including guilt, shame, worry, anxiety, adjustment and adaptation, distress, and empowerment, among others.

Key points

- Genetic counseling should be provided to all individuals with heritable lipid disorders before genetic testing.
- Genetic counseling is a process that includes risk assessment, anticipatory guidance, family-based care, and psychological assessment.

b) What is the ideal way to communicate the benefits and risks of genetic testing to patients?

Uptake of genetic testing should be a shared decision between the patient and the provider, with the clinician not only providing factual details and implications for family members, but also helping patients incorporate this information into their personal situation.[62] Many factors affect an individual's perception of risks vs benefits, including previous experiences, beliefs, and values.[63] Consequently, it is imperative that the discussion incorporates both factual and psychological implications of testing to facilitate a truly informed decision.

Key points

- Communicating the risks and benefits of genetic testing should include a discussion of both the empirical details and the psychological aspects.
- The information provided needs to be tailored to the patient's specific circumstances, level of understanding, and literacy.

c) How do I counsel my patient about genetic test results?

Results should be disclosed either in person or by telephone (a secure virtual consulation may also be considered). The discussion should include both disclosure of the results and implications for family members. The managing clinician should conduct a separate discussion of medical management, if needed.[9] Receiving a genetic test result can be more than just a molecular diagnosis, so the discussion should also include exploration of psychological ramifications and resources for patients and their families.[64] Certified genetic counselors are uniquely trained to help patients understand both the medical and psychosocial implications of a result,[65] and therefore, should be utilized if possible. Contacting a certified genetic counselor by geographic region can be initiated from the following website link: https://www.nsgc.org/page/find-a-genetic-counselor.

Key points

- Genetic test results should be disclosed by a clinician with expertise in genetics, such as a genetic counselor or a clinical lipid specialist who treats individuals and their families with genetic lipid disorders
- The discussion should include both the psychosocial and medical implications of the result.

d) If my patient has a genetic dyslipidemia, should family members also be screened?

It should be recommended that at-risk relatives at least be screened biochemically if a patient has a monogenic dyslipidemia. Cascade testing with either a lipid profile or DNA analysis cost-effectively identifies additional affected individuals in families with many genetic conditions using systematic family tracing. Given that some hereditary dyslipidemias have reduced penetrance, DNA analysis may be preferred in some cases. Cascade testing should begin with first-degree relatives (parents, siblings, and children) and then extend to second- and third-degree relatives in a stepwise "cascade" fashion, moving through the pedigree in sequential steps as additional family members are diagnosed, and until all affected relatives have been identified. Clinicians should construct a family pedigree, identify at-risk relatives, and discuss with the proband the importance of informing relatives about their dyslipidemia and associated risk.[66] Assessment and recommendation should be documented by the clinician. Probands should communicate their diagnosis to at-risk relatives so their relatives have the benefit of knowing their risk and taking steps, such as cascade testing and follow-up treatment, if affected. Communication assistance tools, such as family letters and online tools, should be provided to probands to assist them in sharing their

diagnosis and risk information with relatives; these have been shown to be effective.[67]

Key points

- Cascade testing is a cost-effective way to identify individuals with genetic dyslipidemias.
- Clinicians should recommend to their patients that they communicate their diagnosis, including genetic testing results, to at-risk relatives.
- Probands should communicate their diagnosis and results to their at-risk relatives. Tools exist to assist probands with such communication.

e) What about insurance discrimination and confidentiality?

Once an individual undergoes clinical genetic testing, the results become part of their medical record, unless testing is research based. In many cases, GINA protects against discriminatory use of these results by health insurance companies and employers. However, as mentioned previously GINA does not apply to life insurance companies or long-term disability companies, so a positive test result, especially in individual who has no clinical features, could affect their ability to obtain these types of insurance.[51] In the United States, the Health Insurance Portability and Accountability Act (HIPAA) requires that clinicians keep patients' test results, including genetic test results, confidential in most cases.

Key points

- GINA protects most individuals from genetic discrimination by their employers and/or their health insurance company. It does not apply to life insurance or long-term disability insurance companies.
- The Health Insurance Portability and Accountability Act requires confidential management of medical records.

Summary table of recommendations from the NLA expert panel on genetic testing

Based on our search strategy, literature review, consultations, and writing process, we provide a list of key recommendations related to genetic testing in lipid disorders, shown in Table 4.

Conclusions

In selected patients, genetic testing can be an informative aid in clinical diagnosis. Other potential benefits of genetic testing include guiding optimal management and prevention strategies, advancing care strategies beyond currently available treatments, identifying affected family members, and contributing to scientific progress. The decision to undergo genetic testing in a particular patient with dyslipidemia should weigh the following factors: 1) baseline clinical suspicion of a genetic etiology, 2) expected benefits and risks of testing, and 3) patient values and preferences. Genetic counseling is recommended before and after genetic testing. Understanding the limitations of genetic testing techniques is also important, as is their careful interpretation, to achieve the greatest benefit.

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Table 4 Recommendations for genetic testing in patients with dyslipidemia

Recommendation	Class (strength)	Level of evidence
Principles of genetic testing—counseling		
1. Before ordering a genetic test, it **is recommended** to obtain informed consent and counsel the patient about the benefits and risks of genetic testing.	I	C-EO
2. After a positive genetic test result, it **is reasonable** to provide genetic counseling to patients and their family through either a skilled clinician or a certified genetic counselor.	IIa	C-EO
3. After a negative genetic test result, it still **may be reasonable** to provide genetic counseling to a patient through either a skilled clinician or a certified genetic counselor.	IIb	C-EO
Genetic testing in patients with dyslipidemia		
4. Direct-to-consumer genetic tests are **not recommended** or appropriate for clinical use in dyslipidemia.	III (No benefit)	C-EO
5. Polygenic scores for dyslipidemias are not yet standardized and are currently **not recommended** or appropriate for clinical use in dyslipidemia.	III	C-EO
Genetic testing for monogenic lipid disorders		
6. Genetic testing **is reasonable** when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone.	IIa	B-NR
7. Cascade screening for FH either by lipid profile or genetic testing **is recommended** in all first-degree relatives (children and siblings) of an individual who has tested genetically positive for FH.	I	C-EO
8 Genetic testing for other monogenic lipid disorders (Table 3) **is reasonable** when an accurate diagnosis may affect treatment choice or outcomes.	IIa	C-LD
9. Genetic testing in severe hypertriglyceridemia (SHTG) is generally **not indicated** because most SHTG is polygenic or multifactorial.	III	C-EO
10. Genetic testing in severe hypertriglyceridemia **may be reasonable** if a monogenic disorder is suspected clinically such as familial chylomicronemia syndrome (eg, young age, failure to thrive, relapsing pancreatitis, and absence of secondary causes).	IIb	C-EO

EO, expert opinion; NR, nonrandomized; LD, limited data.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jacl.2020.04.011.

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