95th percentile harbor an identifiable mutation. We similarly identified such a mutation in only 2% of adults, ascertained solely on the basis of an observed LDL cholesterol level of at least 190 mg per deciliter (approximately 5 mmol per liter).[1]

However, we question the authors' statement that "a person who has a familial hypercholesterolemia mutation but does not have a raised cholesterol level is unlikely to have an excess risk of cardiovascular disease." We recently determined that for any given observed LDL cholesterol level, those with a familial hypercholesterolemia mutation are at substantially increased risk for coronary artery disease as compared with those without a mutation.[1] It is likely that this increased risk reflects increased cumulative exposure to LDL cholesterol mediated by a genetic mutation that has been present since birth.

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Dr. Khera reports receiving consulting fees from Amarin and Merck; and Dr. Kathiresan, receiving grant support from Bayer Healthcare Pharmaceuticals and Amarin, holding equity in San Therapeutics and Catabasis Pharmaceuticals, and receiving fees for serving on advisory boards from Bayer Healthcare Pharmaceuticals, Catabasis Pharmaceuticals, Regeneron Genetics Center, Merck, Celera, Genomics, Novartis Pharmaceuticals, Sanofi, AstraZeneca, Alnylam, Eli Lilly, Leerink Partners, Noble Insights, and Ionis Pharmaceuticals. No other potential conflict of interest relevant to this letter was reported.

1. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol 2016;67:2578-89.

DOI: 10.1056/NEJMc1615365

TO THE EDITOR: In their prospective study of screening for familial hypercholesterolemia in childhood, Wald et al. adopt a more relaxed case definition than did Wald and his fellow authors in their earlier meta-analysis of case–control data.[1] In defining a case as either carriage of a familial hypercholesterolemia mutation or a persistently high cholesterol level, the authors risk mixing polygenic hypercholesterolemia with monogenic familial hypercholesterolemia.[2,3]

The use of cholesterol both in the test and the case definition also complicates the assessment of screening performance. In a more orthodox subsidiary analysis (see Table S3 in the Supplementary Appendix of Wald et al. [Oct. 27 issue]), the detection rate for a familial hypercholesterolemia mutation was lower and the false positive rate higher than previously estimated.[1] However, the high biochemical false positive rate could be mitigated by the next-generation sequencing of four genes known to cause familial hypercholesterolemia in samples that exceed the threshold for cholesterol screening.

Such a two-stage screen would detect carriers of familial hypercholesterolemia with the highest cholesterol levels (and the greatest risk of coronary disease), allow mutation-based testing of first-degree relatives, and avoid screening for polygenic hypercholesterolemia, for which conventional treatment is based on absolute risk. Lowering the cholesterol-screening threshold would increase the sequencing burden but would also increase the detection rate for mutation-positive familial hypercholesterolemia without compromising the overall rate for false positives.

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No potential conflict of interest relevant to this letter was reported.

1. Wald DS, Bestwick JP, Wald NJ. Child-parent screening for familial hypercholesterolaemia: screening strategy based on a meta-analysis. BMJ 2007;335:599.
2. Talmud PJ, Shah S, Whittall R, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. Lancet 2013;381:1293-301.
3. Futema M, Shah S, Cooper JA, et al. Refinement of variant selection for the LDL cholesterol genetic risk score in the diagnosis of the polygenic form of clinical familial hypercholesterolemia and replication in samples from 6 countries. Clin Chem 2015;61:231-8.

DOI: 10.1056/NEJMc1615365

THE AUTHORS REPLY: Dividing familial hypercholesterolemia mutations into the categories of pathogenic and nonpathogenic is necessarily imprecise and often arbitrary. The main indicator of pathogenicity is probably the extent to which a familial hypercholesterolemia mutation is associated with a high LDL (or total) cholesterol level, since it is the high LDL cholesterol level that increases the risk of myocardial infarction. Our study, unlike the database noted by Kullo and Safarova,[1] was based on an unselected population and therefore provided an unbiased indicator of the prevalence of familial hypercholesterolemia mutations in persons without high cholesterol levels. Our results and the database both show that a substantial proportion of people with fa-