Clinical Chemistry

Perspectives on Identifying and Treating Familial Hypercholesterolemia in Childhood

Article:
Sarah de Ferranti, Dhruv Kazi, Kirsten Bibbins-Domingo, Stephen Daniels, Barbara Howaniec, Amit Khera, Thomas Newman, and Louis Vernacchio.
Perspectives on Identifying and Treating Familial Hypercholesterolemia in Childhood.
Clin Chem 2021; 67:10 1312-17 https://doi.org/10.1093/clinchem/hvab157

Guest: Dr. Sarah de Ferranti is the division chief of ambulatory cardiology at Children's Hospital Boston and an associate professor of pediatrics at Harvard Medical School.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Familial hypercholesterolemia is a common genetic disorder with catastrophic long-term consequences. In these cases, insufficient low-density lipoprotein cholesterol uptake by hepatocytes results in very high concentrations of serum LDL cholesterol and an increased risk of premature atherosclerotic cardiovascular disease. Detecting and treating this condition early may prevent future acute myocardial infarction, ischemic cardiac arrest, and ischemic stroke.

Familial hypercholesterolemia is currently one of only three tier one conditions identified by the U.S. Centers for Disease Control and Prevention as high priority for genomic screening in the general population. While there has been an emphasis in the U.S. to screen for lipid disorders in general, there are no recommendations to screen children and specifically for familial hypercholesterolemia. Despite its public health importance, familial hypercholesterolemia screening is not widely performed in pediatric practice and genetic testing has not yet been integrated into screening and broad pediatric FH screening approaches have not been formally evaluated in the U.S.

To address this issue in a Q&A feature appearing in the October 2021 issue of *Clinical Chemistry*, six invited experts examined a number of perspectives on identifying and treating familial hypercholesterolemia in childhood. The moderators of that Q&A feature are Sarah de Ferranti and Dhruv Kazi. Please to have Dr. De Ferranti with us on this podcast. She is the division chief of ambulatory cardiology at Children's Hospital Boston and an associate professor of pediatrics at Harvard Medical School. So Dr. de Ferranti, cholesterol screening in childhood has been a controversial topic for decades. Why is that and why talk about it now?

Sarah de Ferranti: Well, child screening has been recommended in childhood for at least three decades with the goal being to reduce the risk of heart attack and other atherosclerotic disease by identifying children at risk and intervening during childhood to lower their cholesterol and hopefully reduce the overall population burden. However, because of the long lead time between the exposure of high cholesterol and the clinical outcome of heart attack or stroke, it's been very difficult to demonstrate a clear benefit for any one particular strategy for screening for lipid disorders. When guidelines are put together, they usually rely on randomized controlled trial data but conducting a trial that needs to last several decades for the clinical outcome to happen is really untenable. And so we haven't been able to prove one way or another clear benefits or harms related to cholesterol screening, and this has been a sticking point for the U.S. Preventive Service Task Force and others who rely on randomized controlled trials' data to underpin their guidelines.

Bob Barrett: So why focus on screening for familial hypercholesterolemia and why in childhood?

Sarah de Ferranti: So, we have become increasingly aware of the importance of familial hypercholesterolemia as a key determinant for premature heart disease. Familial hypercholesterolemia is a known risk factor, at least very severely elevated LDL cholesterol and premature heart disease, particularly affecting those in young adulthood. It's pretty common (present in one in 250 individuals); we are now estimating and can be modified by lots of medications now with good safety profiles in adults.

We think it's really important to separate screening for familial hypercholesterolemia which has clear treatments and a reasonable underpinning of evidence to support early treatment from the other types of lipid disorders that might be identified during childhood that might be milder and for which we have less clear evidence one way or another about whether a medication or lifestyle has a significant benefit on clinical outcomes decades later.

We also like identifying FH or familial hypercholesterolemia early in childhood because if you grow better able to do that than in adulthood and that is because the LDL levels that are seen in those individuals with FH are more clearly delineated from the LDL levels in children without FH, particularly

around the age of 10. So it's a good time to identify these children with FH.

Bob Barrett: What were some of the most interesting or unexpected perspectives that came out of this Q&A roundtable?

Sarah de Ferranti: Well, some of the interesting perspectives really came from the diversity of attendees. We were able to include a parent of a child who had FH, some researchers, including those really embedded in the field as well as those who are skeptics, an adult cardiologist who focuses on genetics, really a diversity of opinions and so that was the real benefit to the discussion.

One point that came out was an interesting one which was: it's been our habit or our practice to screen for lipid disorders multiple times during childhood to increase our possibility of identifying these children. But if you are looking for a genetic disease, it should perhaps make sense just to screen once because you either have it or you don't. So that was an interesting insight and it really goes along with pulling out screening for FH from general lipid screening during childhood. Another key point that came up was really a focus on disparities and genetic diseases, with two points being made: one that this familial hypercholesterolemia can be identified by a gene test but that might of limited availability (particularly if it's not covered by insurance even if it should be). And then second question is around the types of genes that have been identified. Many of our research to date, our genetic research has really been done in European ancestry populations and really hasn't investigated FH in non-white populations. And so that really will limit our ability to come up with a test that diagnoses FH in these populations. So we really need to do more research on the topic.

Bob Barrett: Doctor, what should we take away from this discussion in terms of current clinical practice?

Sarah de Ferranti: I think one key point to take away from this discussion is really thinking clearly about whether you are screening for FH or screening for other lipid disorders when you see a patient. And if there is a family history that is suggestive or a very high cholesterol or premature heart disease, you're really thinking about screening for FH and you might be able to intervene if you identify it early enough. You know, from a T-paper published in the New England Journal several years ago that early treatment of individuals with FH

starting around age 10 really can modify the clinical course, particularly when compared to their parents, and really reduce rates of heart disease compared to their parents who didn't get that early treatment. So we want to find these individuals early, but you really have to think about how you're screening for FH in particular.

And then the other point might be to consider a non-HDL as a screen, it's a simple test that doesn't need to be done fasting to really make it as easy as possible. But we will probably have to consider different non-HDL cup points than LDL cup points. There are some technical things about how exactly to do this in a way that maximizes participation on the part of these children and families.

And then the third point might be to that we need to consider how best to include genetic testing in our regimen. So our first screening test would probably be a lipid one. Certainly, we're not going to start with genetic testing unless the family already has that gene known in their family. But we would want to use our genetic tools to really identify those who have those causative genes who would benefit most from early treatment with medication and also early optimization of lifestyle to prevent other risks from acquiring.

Bob Barrett: Oh finally, Dr. De Ferranti let's look ahead: where do you think to feel this headed, and what do you think this practice will look like in five or even 10 years from now?

Sarah de Ferranti: I think the field is headed in a very good direction that will improve the health and outcomes of individuals with FH and now that we understand that one in 250 are affected, and maybe even higher prevalence in some, some populations where the prevalence has enriched related to backgrounds and founder effects.

It's really important that we find these individuals early and ideally at the time where we would recommend lifestyle and statin therapy. I think the field is headed towards teasing that FH screening out from the other lipid disorders which also require treatment with lifestyle modification advice or other therapies. But we want to keep this difference in mind and I know we're going in that direction.

The other thing is we're using new models, new modeling techniques to try to project what would be benefits of different strategies for screening and treatment because we can't wait around for individuals

to have these outcomes, these critical outcomes, but we can try to tease together what lipid profiles look like over time and what the impact of different types of treatments and at different times would do in terms of benefit and for lowering LDL cholesterol and clinical benefit.

I think also that we're further focused on better understanding FH-causing gene mutations in non-white populations and how we can really optimize identification and treatment in populations that had been affected negatively by lack of treatment or lack of identification and thus higher rates of premature heart disease.

Bob Barrett: That was Dr. Sarah de Ferranti, the division chief of ambulatory cardiology at Children's Hospital Boston and an associate professor with pediatrics at Harvard Medical School. She served as moderator of the Q&A feature in the October 2021 issue of *Clinical Chemistry* on identifying and treating familial hypercholesterolemia in childhood. I'm Bob Barrett. Thanks for listening.