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Cascade Screening for Familial Hypercholesterolemia and the Use of Genetic Testing

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Familial hypercholesterolemia

(FH) is a dominantly inherited genetic disorder affecting approximately 1 in 250 individuals. It is characterized by markedly elevated low-density lipoprotein cholesterol (LDL-C) and accelerated atherosclerotic cardiovascular disease (ASCVD).[1] Persons with FH have a 2.5- to 10-fold in-creased risk of ASCVD com pared with controls, but when FH is diagnosed and treated early in life, the risk is greatly reduced (≈ 80%).[1] However, most people with FH have never been diagnosed or treated. Active case finding of FH plus family-based cascade screening can help identify individuals with FH and ensure treatment before ASCVD onset.

How Cascade Screening for FH Works

Because FH is dominantly inherited, cascade screening of family members can be highly effective. Cascade screening relies on identifying an FH patient (proband) and active cholesterol testing, genetic testing, or both for all potentially affected relatives–a cycle that is repeated (cascaded) for each relative diagnosed with FH, thereby expanding the number of potential cases detected. Case identification requires that a clinician suspect diagnosis based on established clinical criteria[1]; the diagnosis may be supported by genetic testing (sequencing) of the 3known FH genes(*LDLR,APOB,PCSK9*),which identifies a causal mutation in 60% to 80% of cases suspected clinically to represent FH. Use of the *International Classification of Diseases, Tenth Revision* code for FH diagnosis (E78.01) and family history of FH (Z83.42) can facilitate case finding using electronic health records (EHRs). In concept, cases of FH could also be identified through the application of algorithms to EHR, laboratory, and billing code data or through large-scale DNA sequencing.

Once an index patient with FH is identified, cascade screening starts with first-degree relatives (parents, siblings, children). If the affected parent is found, as many relatives as

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possible on that parent's side of the family should be screened. Children of the affected parent's siblings should be screened also because treatment in childhood is indicated for those who are affected. Each new FH case found via cascade screening then becomes a proband for broader cascading (Figure).[2,3]

Screening can be done via cholesterol testing, genetic analysis, or both.[1] Because LDL-C levels between FH and non-FH patients can overlap (especially in adults), approximately 20% of family members with *LDLR* mutations but modestly elevated LDL-C will remain undiagnosed if only LDL-C levels are obtained.[4] Hence, identification of a pathogenic FH mutation in the proband yields a tool for the unambiguous cascade screening in the family, and incorporating genetic testing into cascade screening improves the detection rate for FH.However, the inability to identify a specific mutation does not rule out the formal diagnosis of FH.

Cascade screening can reduce the average age at which individuals with FH are diagnosed and increase the percentage of individuals receiving lipid lowering therapies, potentially resulting in reductions in LDL-C and ASCVD.[5] Cascade screening in the Netherlands identified, on average, 8 relatives with FH for each index case[5] and significantly increased the proportion of FH patients receiving treatment.[5]The SAFEHEART program in Spain showed that genetic screening identified patients at a younger age (median age, 49.5 years) and improved treatment initiation and adherence.[6]

Clinical and Public Health Considerations

One barrier to cascade screening for FH in the United States (where current estimates are that less than10% of FH cases have been identified), is the challenge of identifying the index patient.Amongadults, universal cholesterol screening recommendations have not fully been adopted. Lipid testing in children is more discriminative for FH than in adults, which is a rationale for lipid screening in childhood[1] (although the United States Preventive Services Task Force found insufficient evidence to support this practice).[7] However, arecent study demonstrated the efficacy of screening children for FH during routine immunization visits, using cholesterol levels and genetic testing (for every1000 children screened, 8 with FH were identified [4 children and 4parents]).[3] Another potential strategy for index case identification uses machine learning techniques to mine EHR, laboratory, and billing code data (Figure) to highlight individuals with characteristics consistent with FH for formal identification by a physician. Large-scale DNA sequencing can identify FH cases that were not diagnosed clinically and wouldnot have been detected through an algorithmic approach.[8]

A second barrier is the process of cascading from the index case in the US health care system, because privacy concerns mandate that the proband make the first contact with family members. A randomized clinical trial is underway to determine if identification of probable FH probands through a search of EHR data leads to cascade screening if probands receive genetic testing results and counseling to contact relatives about their risk of FH.

From a patient perspective, it is important that the diagnosis of FH does not result in discrimination. In the United States, the Genetic Information Nondiscrimination Act

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provides protection against6 health insurance and employment discrimination;however, there is currently no protection against bias for life insurance or disability insurance.

Cost-Effectiveness of FH Cascade Screening

FH cascade testing strategies incorporating genetic testing results when available or LDL-C when genetic testing results are not available are cost-effective for identifying new cases of FH.[9] The genetic screening program in the Netherlands found that, on average, 3.3 years of life were gained for each new case diagnosed (cost, $8700/y of life gained).[9] Recent data suggest an incremental cost-effectiveness ratio of $2500 to $4500 per quality-adjusted life-year gained.[10] The current costs for testing for *LDLR*, *APOB*, and *PCSK9*mutations are still significant ($500-$1500).However, the costs are likely to decrease, partly due to the use of next-generation sequencing, and testing is often covered by insurance.

Evidence Base for FH Cascade Screening

Cascade screening for FH is highly effective and has been recommended by national[1] and international bodies.[6] Based on the overall evidence, the Centers for Disease Control and Prevention classifies cascade screening for FH as a tier1genomic application, with evidence-based recommendations (grade A) based on systematic reviews that support integration into clinical and public health programs.

Bottom Line

Cascade screening for FH is an evidence-based intervention that can reduce the burden of morbidity and mortality from ASCVD in populations. Individual physicians, health care systems, and public health organizations should integrate cascade screening into routine care.

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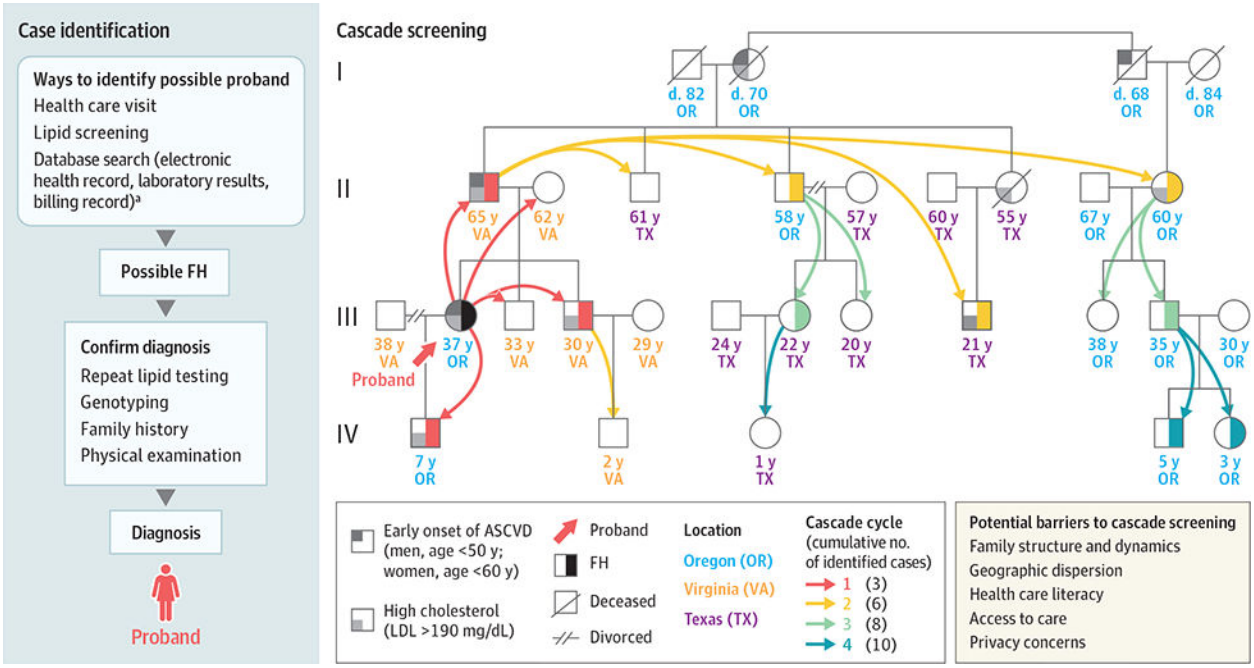

Figure. Process From Case Identification to Cascade Screening

Proband identification can also occur through childhood immunization visits,[2] systematic lipid testing (eg, testing all employees in an organization), or recommended lipid testing (eg, universal screening for adults). Cascade screening begins once the proband has been identified. Next, several steps of cascade screening are needed to identify all patients with familial hypercholesterolemia (FH). Color of shaded segment for FH indicates the cascade cycle during which the affected individual was identified.

[a] Source, Safarova et al.[3]