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Integrating Patient-Reported Outcomes Into Clinical Genetic Testing for Familial Hypercholesterolemia

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Abstract Patient-reported outcomes (PROs) and PRO measures (PROMs) are often used to help clinicians and researchers understand patients' personal concerns, feelings, experiences, and perspectives following the implementation of an intervention. Notably, PROs and PROMs can inform health systems, health policy, and payers on the utility of clinical genetic testing based on each patient's personal values, perspectives, and potential health behaviors subsequent to testing. In this topic synopsis, we discuss the underexplored role of and implications for PROs and PROMs following genetic testing for familial hypercholesterolemia (FH), an autosomal dominant genetic disorder of cholesterol metabolism that can lead to highly premature fatal and nonfatal myocardial infarction and stroke. We also discuss why the use and consideration of patient perspectives, via PROs and PROMs, are critical to the process of optimizing patient care across various FH treatment contexts. As expert clinician groups consider the latest evidence when establishing recommendations for FH genetic testing, there is a ripe opportunity for clinicians and researchers to explore the value and utility of PROs to inform and possibly improve care for patients diagnosed with FH. (*J Patient Cent Res Rev.* 2021;8:336-339.)

Keywords patient-reported outcomes; genetic testing; familial hypercholesterolemia; implementation science; cardiovascular disease

Utility and Value of Patient-Reported Outcomes to Inform Clinical Care and Quality

Patient-reported outcomes (PROs) and PRO measures (PROMs) can help clinicians and researchers understand and document patients' personal concerns, feelings, experiences, and perspectives regarding an intervention. Such data can also offer evidence to inform clinical guidelines, clinical research, insurance coverage policies and reimbursement decisions, health product development, health system policies and protocols, and standards of care.[1-4] PROs are often context-driven and specific to disease, indication, and context, allowing PROs to precisely inform clinical practice. However, PROs following clinical genetic testing are not well defined or structured.

Dobrozsi and Panepinto proposed a conceptual framework to incorporate PROs as measures that define, from the patient perspective, patient symptoms and function, with the goal of tailoring patient therapies, improving patient outcomes, improving patient-provider communication, and improving health care provider quality and performance.[5] This conceptual framework, as it applies to clinical genetic testing for various familial diseases, might be used to inform health systems, health policy, and payers on the utility of clinical genetic testing based on patients' personal values and perspectives as well as their health behaviors subsequent to testing.

One such intervention that is underexplored from a PRO standpoint is genetic testing for familial hypercholesterolemia (FH). FH is an autosomal dominant genetic disorder of cholesterol metabolism characterized by very high levels of low-density lipoprotein (LDL) cholesterol from birth, leading to highly premature fatal and nonfatal myocardial infarction and stroke.[6] It affects an estimated 1 in 200 to 1 in 500 individuals, or 1.3 million people, in the United States; among those in whom a positive genetic test occurs, individuals with markedly elevated LDL cholesterol (ie, LDL-C of >190) have a significantly greater risk of mortality due to an adverse cardiovascular event.[6,7]

More than 1200 different mutations of LDL have been described and can be divided into 6 different classes, each affecting a particular aspect of LDL function.[8] Classes

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include: synthesis of precursor LDL receptors; processing of LDL receptor in the Golgi body or endoplasmic reticulum; abnormal LDL binding; defective clathrin-mediated endocytosis of LDL receptor; increased LDL receptor degradation (ie, increased proprotein convertase subtilisin/kexin type 9 [PCSK-9] activity); and inability of LDL receptor to attach to the cell's basolateral membrane.[8] Another way to approach the LDL cholesterol metabolism concerns that occur in those with FH is to determine whether there is a defect in the LDL receptor or the complete absence of the LDL receptor, the latter of which presents with a more severe phenotype.[8]

In the United States, prevalence differs among races; for instance, the frequency of heterozygous FH is around 1 in 250 among White and Black individuals, whereas for Mexican American individuals and individuals of other races (collectively), it is around 1 in 414 and 1 in 343, respectively.[7] Homozygous FH is far rarer, occurring around 1 in 1,000,000 people.[9] Among certain geographic or ethnic populations, this frequency can be higher. For instance, in French Canadian individuals residing in Quebec, the estimated rate is around 1 in 275,000.[10] In addition to ethnic differences affecting the prevalence rate of FH, gender and racial differences contribute to health disparities among groups of individuals with this genetic disease.[11] For instance, being a female and/or of Asian or African descent is independently associated with a decreased likelihood of achieving LDL-C treatment goals, as compared to White patients.[11] The Dutch Lipid Clinic Network (DLCN) and the Simon Broome Register (United Kingdom) diagnostic criteria for heterozygous FH both take into account family history, physical examination findings, and lipid profiles.[6] These diagnostic criteria are not applicable to the pediatric population, and they may miss patients with only mild manifestations of heterozygous familial hyperlipidemia.[6] Genetic tests, including gene panel testing and exome sequencing, can be conducted to look for variations in the LDL receptor, apolipoprotein B, and *PCSK9* genes.

PROs Pertaining to Opting for Familial Hypercholesterolemia Genetic Testing

Statins have been available for many years and have effects in lowering cardiovascular disease event risk.[12,13] Recommendations for lifestyle management include exercise, a diet low in saturated fat and cholesterol, and smoking cessation counseling.[14] A 50% reduction in LDL-C is a minimum goal for all patients with FH.[6] Pharmacological therapy includes statins, which are usually used in combination with ezetimibe, bile acid sequestrants, or PCSK9 protein inhibitors.[6] Treatments for refractory cases in patients with the homozygous form of FH include lomitapide (inhibitor of microsomal triglyceride transfer protein large subunit) and mipomersen (antisense oligonucleotide that inhibits translation of apolipoprotein B messenger RNA).[15] A twice-yearly injection of inclisiran, a small interfering RNA for PCSK9, was shown to have significant LDL-C reduction results in adults with heterozygous FH in a phase 3 clinical trial (ORION-10).[16]

The use and consideration of patient perspectives are critical to the process of optimizing patient care across these FH treatment contexts.[6] In a previous publication, we reviewed the literature for studies that reported key clinical and nonclinical outcomes following FH genetic testing[17] and found that reported PROs were described in two studies as "1) concerns about receiving genetic test results, and 2) out-of-pocket costs associated with FH genetic testing."[18,19] Our review also showed that the analysis and structure of PRO reporting across these two studies were vastly different.

Only 2 of 21 studies included in our literature review reported PROs,[18,19] and only 1 of those 2 reported race/ethnicity data (for which all 7 study participants were White).[19] Pang et al qualitatively explored why some parents declined genetic testing for their children and identified the parent's concerns about possible stigmatization due to genetic testing,[18] while Jones et al conducted interviews with 7 patients to understand the patients' overall experiences in receiving FH genetic test results.[19] The study conducted by Jones et al was on behalf of Geisinger Health's MyCode Community Health Initiative, a pioneering study out of Pennsylvania that is 1) returning actionable results or secondary findings following whole exome sequencing of study participants, and 2) considering or collecting information about how participants cope with their results (eg, anxiety or distress) as well as participants' readiness to engage in recommended care.[19,20]

Aside from our published literature review, a case study revealed serious FH treatment limitations following reliance on the (U.S.) Make Early Diagnosis to Prevent Early Deaths (MEDPED), Simon Broome, or DLCN criteria alone or absent FH genetic testing or other emerging clinical criteria.[21] Particularly, Mudgundi et al described a clinical case wherein a patient was diagnosed with possible FH after failing to meet Simon Broome, DLCN or MEDPED criteria, but rather by meeting the American Heart Association diagnosis recommendation. FH genetic testing was considered only after learning that a patient's insurer would deny coverage for a PCSK9 inhibitor unless the clinician provided to the insurer evidence of a causal FH genetic mutation.[21] DeAngelis et al also showed

similar patient concerns and perspectives, including the emotional impact of having FH and having interactions with insurance companies regarding coverage of FH treatments (ie, PCSK9 inhibitors) that may be predicated on positive FH genetic test results.[22]

Proposed Targets for Future Research

PROs following FH genetic testing are largely understudied and not well defined conceptually to inform patient management plans and decisions. As covered in the preceding sections, few studies have included both PROs and clinical outcomes following FH genetic testing, and PRO data collection methods and reporting are largely unstructured.[18,19] Increased and coordinated efforts among key stakeholders in the FH community are necessary to conduct more structured analyses of the patient/clinician experience with FH genetic testing. These are important to gain a deeper understanding about how and the extent to which patients with FH must navigate systemic, emotional, and other humanistic factors and barriers related to FH genetic testing and subsequent FH management and treatment in partnership with their caregivers. This is particularly true for racial-minority patients, who are at risk of being undiagnosed or underdiagnosed and who must navigate structural barriers, biases, and complexities among and across health systems globally to access clinical genetic testing, receive test results, and affordably engage in care management based on those results.

The American College of Cardiology recommends that genetic testing for FH should be offered to individuals of any age suspected of FH based on the examination of their clinical or family histories.[23] Currently, there are important considerations surrounding this recommendation for FH genetic testing conducted within the United States and other similarly situated countries. First, the ratio of barriers to facilitators toward the clinical implementation of FH genetic testing in the United States is high.[24] Second, FH is heavily underdiagnosed — especially among non-White populations in the United States[17] — due to limited physician knowledge and experience with the disorder and unclear guidelines around the appropriate use of FH genetic testing for FH diagnosis.[25] Third, FH is associated with premature heart disease, a disease that was the leading cause of death in the United States in 2017, rendering FH genetic testing a potential clinical diagnostic tool to help identify and confirm FH early or upon initial clinical suspicion.[26]

Summary

Based on the existing literature on patient-reported outcomes involving genetic testing of familial hypercholesterolemia, we recommend that clinicians and researchers: 1) understand the clinical limitations of relying on Simon-Broome, MEDPED, or DLCN criteria without confirmatory FH genetic testing; 2) identify existing contributing factors within their practices by determining the role FH genetic testing plays as either a barrier to or facilitator of effective FH management; and 3) identify, define or develop, and apply emerging PRO or PROM collection frameworks or concepts[5,27] to methodologically collect patient perspectives that can offer robust insights into diverse patient journeys following FH genetic testing.

Patient-Friendly Recap

- Patient-reported outcomes (PROs) can be used to tailor care plans to individual preferences, though little is known about PROs pertaining to clinical genetic testing.
- Authors reviewed the literature on genetic testing for familial hypercholesterolemia (FH), a genetic disorder that can lead to deadly cardiovascular disease, to explore how various PROs within the scope of FH genetic testing might affect patient management.
- Clinicians should be aware that relying on standard FH diagnostic criteria without confirmatory genetic testing may hinder certain treatment coverage by insurers. Future research can apply emerging measures of PROs to study the diverse journeys traveled by individuals with FH.

Author Contributions

Study design: all authors. Manuscript drafting: all authors. Critical revision: all authors.

Conflicts of Interest

Christine Lu reports a contractual arrangement with Massachusetts General Hospital's Center for Genomic Medicine that is unrelated to the work presented herein. Rachele Hendricks-Sturrup is presently employed by the Duke-Margolis Center for Health Policy.

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