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EXPLORING THE EXPERIENCE, CONCERNS AND EXPECTATIONS OF PATIENTS WITH SUSPECTED FAMILIAL HYPERCHOLESTEROLAEMIA (FH) WHEN UNDERGOING GENETIC TESTING: A QUALITATIVE STUDY

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ABSTRACT

Familial Hypercholesterolaemia (FH) is an inherited genetic disorder with an autosomal dominant mode of inheritance. If left untreated, patients with FH are 22 times more likely to have premature coronary artery disease compared to non-FH patients. While FH can be clinically diagnosed using clinical diagnostic criteria, molecular diagnosis is still the gold standard to diagnose FH. However, genetic testing for FH is not widely available in Malaysia except through research. Additionally, the experience, concerns and expectations of patients undergoing genetic testing for FH in this country was not known. Therefore, the objective of this study was to explore the perception, experience, concerns and expectations of patients with suspected FH identified in the Ministry of Health (MOH) primary care clinics who have undergone genetic testing. This study was conducted using the qualitative research method at 11 MOH public primary care clinics in Selangor, Wilayah Persekutuan Kuala Lumpur and Putrajaya from September 2020 to October 2023. A semi-structured in-depth interview was conducted among patients who have received their genetic test results. The interviews were audio-recorded, transcribed verbatim and continued until saturation was achieved. The N-Vivo Qualitative Software (Version 14.3) was used to assist data organisation. Thematic analysis was conducted to identify code, categories, the patterns and themes within the data set. This study interviewed a total of 20 patients. It was revealed that patients' perception and attitude towards genetic testing were generally positive despite their lack of knowledge and awareness regarding genetic testing and FH. Genetic testing was mainly perceived as a mean to provide aetiological explanation of their raised cholesterol level and information about their future risk and preventive measures of cardiovascular disease, as well as treatment and management of FH. It also motivated them to adhere to the lipid-lowering medication especially when they received positive genetic test results. The primary motivators to undergo genetic testing was the free testing opportunities provided under this study. The main barrier was the high cost of the genetic test in the private healthcare setting. Patients expressed the desire for wider accessibility of genetic testing for FH in both the public and private healthcare systems as it would contribute to improve health outcomes. Additionally, patients expected that their genetic test results were delivered by their treating doctors. They also expressed a willingness to make recommendations for genetic testing and cascade screening to close family members as they see it as a moral obligation. Findings from this study indicates the urgent need for the MOH to prioritize early detection of FH and to provide free genetic testing services for patients with suspected FH in the public healthcare system. In order to ensure smooth delivery of genetic testing in the public healthcare system, a clinical practice guideline on the identification and management for FH should be developed and training should be provided to doctors to improve their knowledge and skills in the management of FH. With regards to future research, a cost-effectiveness analysis of genetic testing for FH should be conducted to guide policymakers in the MOH to make an informed decision regarding resource allocation and implementation of genetic testing in the Malaysian public healthcare system.

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CHAPTER 1
INTRODUCTION

1.1 Research Background

Familial Hypercholesterolaemia (FH) is an inherited genetic disorder with an autosomal dominant mode of inheritance [1]. This means that if a person has FH, they have 50% chance of passing it to their children. It is one of the commonest monogenic diseases that leads to an elevated risk of premature atherosclerosis due to its effect on plasma cholesterol levels [2]. FH is commonly caused by mutations in the low-density lipoprotein receptor (*LDLR*) gene, apolipoprotein B (*APOB*) gene and/or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) gene [3], with the most common mutations found in the *LDLR* gene, followed by *APOB* and *PCSK9* genes [4]. Other rare mutations in the LDL receptor adaptor protein 1 (*LDLRAP1*) gene, apolipoprotein E (*APOE*) gene, ATP-binding cassette subfamily G members 5 and 8 (*ABCG5* and *ABCG8*) genes have been reported to be responsible for the recessive form of FH [5, 6].

There are two forms of FH – the heterozygous form (HeFH) in which the patients have one normal allele and one mutated allele; and the homozygous form (HoFH) where patients have two mutated alleles [7]. HeFH is the more common form of FH with a global prevalence estimated to be 1 in 200 to 1 in 500 [8]. A previous study estimated that at least 15 million FH cases could be concentrated in the Southeast Asian and Western Pacific Region [9].

In Malaysia, the prevalence of clinically diagnosed HeFH is estimated to be 1 in 100 [10]. This is higher than the reported global prevalence of 1 in 250 [11] and the highest reported prevalence in the Western Pacific Region [12]. A subsequent study revealed that individuals with molecularly confirmed FH were identified at a rate of 1 in 427 [13]. On the other hand, HoFH is rarely reported [14], with a global prevalence estimated at 1:160,000–300,000 [15]. Patients with HeFH are clinically characterized by plasma cholesterol levels more than 4.9 mmol/L. In contrast, plasma cholesterol levels of HoFH patients are commonly three folds of HeFH, which is >13 mmol/L [16]. Apart from that, premature corneal arcus (<45 years old) and tendon xanthomas