

SECONDARY FINDINGS IN WHOLE EXOME
SEQUENCING: PREVALENCE AND
MANAGEMENT

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AND MANAGEMENT

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DECLARATION

I hereby declare that the work in this thesis is my own except for quotations and summaries which have been duly acknowledged.

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ABSTRAK

Penjujukan keseluruhan eksom (Whole Exome Sequencing, WES) merupakan satu kaedah diagnostik genomik yang digunakan secara meluas untuk mengenal pasti varian genetik yang berkaitan dengan penyakit jarang dan keadaan yang tidak dapat didiagnosis. Selain membantu dalam diagnosis keadaan utama, WES juga boleh menghasilkan penemuan sekunder yang tidak berkaitan dengan indikasi utama ujian, tetapi mempunyai implikasi klinikal yang penting. Walau bagaimanapun, data mengenai kelaziman dan pengurusan penemuan sekunder dalam populasi Malaysia masih terhad. Kajian ini bertujuan untuk menilai kelaziman dan pengurusan klinikal penemuan sekunder yang dikenal pasti melalui WES di Hospital Kuala Lumpur (HKL) dan Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR). Satu audit klinikal retrospektif telah dijalankan melibatkan 882 pesakit yang menjalani WES antara Januari 2021 hingga Mac 2026. Daripada jumlah ini, 790 pesakit memberikan persetujuan untuk menerima penemuan sekunder dan dimasukkan ke dalam analisis, manakala 92 pesakit menolak dan dikecualikan daripada analisis ini. Data diperoleh daripada rekod perubatan yang merangkumi ciri demografi, keputusan ujian genetik, pengelasan penemuan sekunder mengikut garis panduan American College of Medical Genetics and Genomics (ACMG), serta hasil pengurusan klinikal. Analisis statistik deskriptif telah dijalankan. Penemuan sekunder dikenal pasti dalam 33 pesakit daripada 790 individu (4.18%), dengan sejumlah 28 penemuan sekunder direkodkan. Satu pesakit mempunyai dua penemuan sekunder yang berbeza. Daripada varian yang dikenal pasti, 13 (46.43%) diklasifikasikan sebagai patogenik dan 15 (53.57%) sebagai berkemungkinan patogenik. Majoriti penemuan sekunder melibatkan gen yang berkaitan dengan penyakit kardiovaskular dan sindrom kanser keturunan. Pengurusan klinikal lazimnya melibatkan kaunseling genetik dan rujukan kepada pakar, namun terdapat variasi dalam pematuhan susulan dan pengambilan saringan keluarga dalam kalangan ahli keluarga pesakit. Kajian ini memberikan bukti tempatan mengenai beban dan pengurusan klinikal penemuan sekunder yang dikenal pasti melalui WES di Malaysia. Hasil kajian ini menekankan kepentingan laluan susulan yang berstruktur, kaunseling genetik yang berkesan, serta integrasi perubatan genomik yang lebih baik dalam amalan klinikal rutin bagi mengoptimumkan utiliti klinikal penemuan sekunder.

ABSTRACT

Whole exome sequencing (WES) is a genomic diagnostic tool widely used to identify genetic variants associated with rare diseases and undiagnosed conditions. In addition to diagnosing the primary condition, WES may also generate secondary findings that are unrelated to the primary indication of testing but have important clinical implications. However, data on the prevalence and clinical management of secondary findings in the Malaysian population remain limited. This study aimed to evaluate the prevalence and clinical management of secondary findings identified through WES at Hospital Kuala Lumpur (HKL) and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, UKM Children's Specialist Hospital (Hospital TABTAR). A retrospective clinical audit was conducted involving 882 patients who underwent WES between January 2021 and March 2026. Of these, 790 patients consented to receive secondary findings and were included in the secondary findings analysis, while 92 patients opted out and were excluded. Data were obtained from medical records, including demographic characteristics, genetic test results, classification of secondary findings according to the American College of Medical Genetics and Genomics (ACMG) guidelines, and clinical management outcomes. Descriptive statistical analyses were performed. Secondary findings were identified in 33 patients among 790 individuals (4.18%), with a total of 28 secondary findings recorded. One patient harboured two distinct secondary findings. Of the variants identified, 13 (46.43%) were classified as pathogenic and 15 (53.57%) as likely pathogenic. The majority of secondary findings involved genes associated with cardiovascular disorders and hereditary cancer syndromes. Clinical management commonly included genetic counselling and specialist referral, although variability was observed in follow-up adherence and cascade screening uptake among family members. This study provides local evidence on the burden and clinical management of secondary findings identified through WES in Malaysia. The findings highlight the importance of structured follow-up pathways, effective genetic counselling, and improved integration of genomic medicine into routine clinical practice to optimise the clinical utility of secondary findings.

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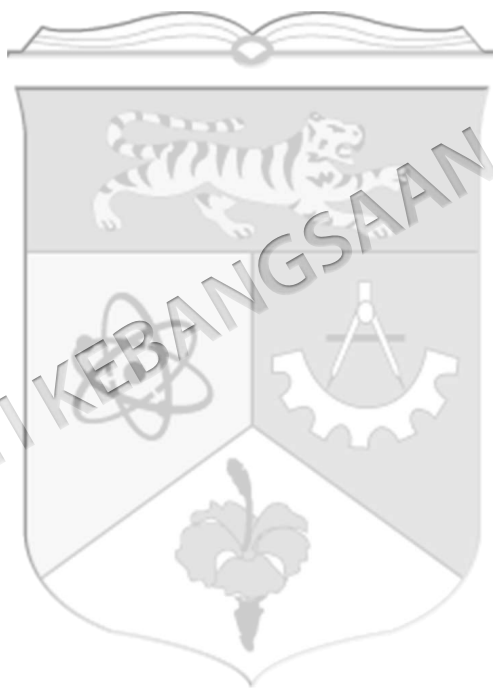
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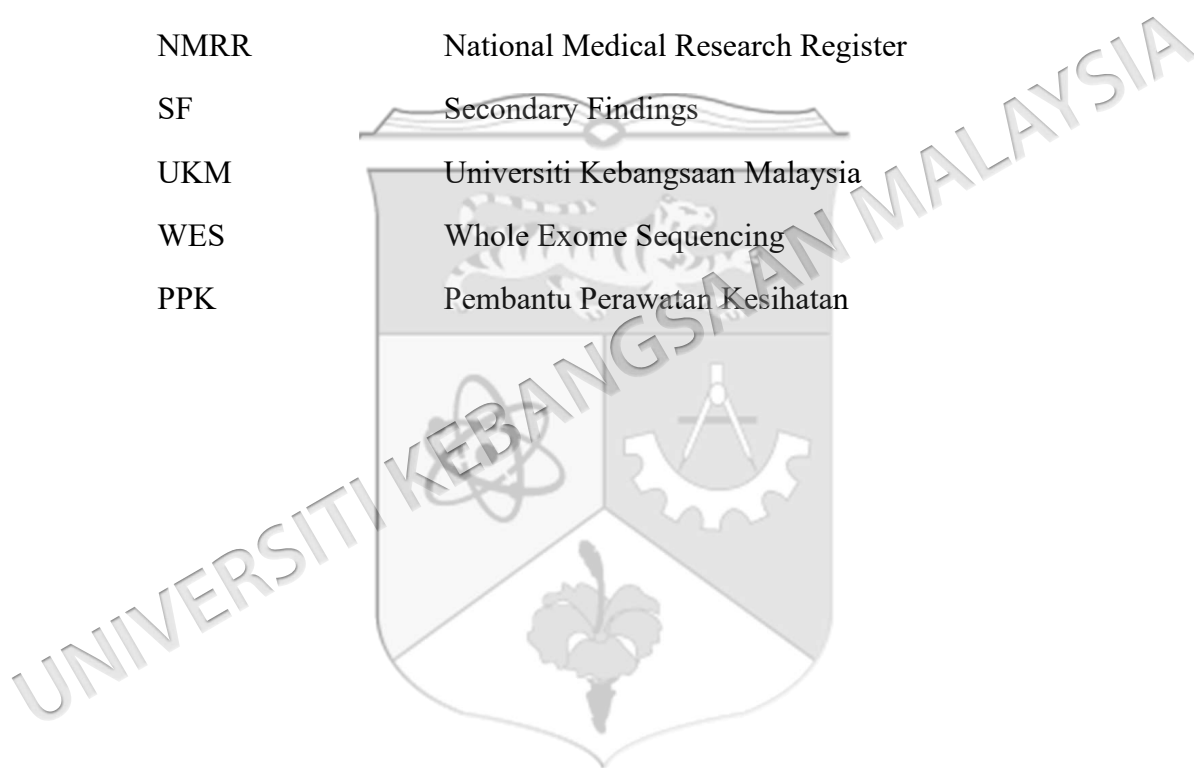
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LIST OF ABBREVIATIONS

ACMG	American College of Medical Genetics and Genomics
HKL	Hospital Kuala Lumpur
Hospital TABTAR	Hospital Tunku Ampuan Besar Tuanku Aishah Rohani Hospital Pakar Kanak-Kanak UKM
JPEUKM	Jawatankuasa Penyelidikan dan Etika Universiti Kebangsaan Malaysia
MELAS	Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes
NMRR	National Medical Research Register
SF	Secondary Findings
UKM	Universiti Kebangsaan Malaysia
WES	Whole Exome Sequencing
PPK	Pembantu Perawatan Kesihatan



CHAPTER I

INTRODUCTION

1.1 RESEARCH BACKGROUND

Genetic testing has become an essential component of modern healthcare, playing a significant role in the diagnosis, management, and prevention of a wide range of inherited and complex diseases (Green & Guyer 2011). With the advancement of genomic technologies such as Whole Exome Sequencing (WES), clinicians are now able to identify pathogenic variants across thousands of genes in a single test, thereby improving the diagnostic yield in patients with suspected genetic disorders (Yang et al. 2014; Miller et al. 2021). However, alongside clinically relevant findings related to the primary indication for testing, genetic analysis may also reveal secondary findings. These are defined as pathogenic or likely pathogenic variants that are unrelated to the original reason for testing but may have important implications for an individual's future health.

Secondary findings may indicate a predisposition to a variety of medically actionable conditions, including hereditary cancer syndromes, cardiovascular disorders, metabolic diseases, and other genetic conditions for which early detection and intervention may significantly reduce morbidity and mortality (Kalia et al. 2016). Recognizing the clinical importance of such findings, the American College of Medical Genetics and Genomics (ACMG) has developed recommendations regarding the reporting of selected secondary findings identified during genomic testing. The most recent update, ACMG Secondary Findings v3.3 (2025), includes a curated list of 84 genes associated with conditions for which preventive measures, surveillance strategies, or therapeutic interventions are available. Importantly, these genes are actively analysed rather than being identified incidentally, and patients are provided

with the option to opt out of receiving secondary findings through the informed consent process.

Current literature suggests that clinically actionable secondary findings are identified in approximately 1–4% of individuals undergoing Whole Exome Sequencing (WES), although the reported prevalence varies depending on the study population, sequencing methodology, and criteria used for variant classification and reporting (Kalia et al. 2016). While these findings may provide substantial clinical benefits through early disease detection, risk assessment, and preventive interventions, they may also introduce psychological, social, and ethical challenges for patients and their families. Studies such as Bombard et al. (2013) have reported varied patient responses following the disclosure of secondary findings, including feelings of empowerment, anxiety, and uncertainty. These findings highlight the important role of genetic counselling in preparing patients for the potential outcomes of genomic testing and facilitating informed decision-making.

In Malaysia, the practice of reporting secondary findings generally follows international recommendations, particularly those established by the ACMG (Lee et al. 2021). However, there is currently limited published evidence describing a standardized national framework governing the disclosure, interpretation, and clinical management of secondary findings identified through genomic testing. Consequently, practices may vary across institutions and clinical settings. Furthermore, the implementation of genomic medicine in Malaysia is influenced by contextual factors such as the limited availability of genetics services, varying levels of genomic literacy among healthcare providers and patients, and cultural perceptions regarding genetic risk, inheritance, and disease susceptibility (Balasopoulou et al. 2017; Omran et al. 2024). Although previous local studies have explored broader challenges in the delivery of genetic services, evidence specifically focusing on the prevalence, disclosure, and management of secondary findings remains limited.

Given these gaps in knowledge, there is a need to better understand how secondary findings are identified and managed in real-world clinical practice within Malaysia. This includes examining the prevalence and spectrum of secondary findings detected through Whole Exome Sequencing, the clinical actions undertaken following disclosure, and their influence on patient management decisions. Therefore, this study aims to evaluate the prevalence and clinical management of secondary findings identified through Whole Exome Sequencing in selected Malaysian tertiary centres, with the goal of generating evidence that may support the development of local guidelines and promote a more standardized approach to genomics medicine in Malaysia.

1.2 PROBLEM STATEMENT

Secondary findings refer to pathogenic or likely pathogenic variants identified during Whole Exome Sequencing (WES) that are unrelated to the primary indication for testing but are considered medically actionable due to their potential implications for disease prevention, early detection, or targeted clinical intervention. These findings may provide significant clinical value by enabling timely surveillance and risk-reducing strategies for individuals found to be at increased genetic risk of certain conditions.

In Malaysia, informed consent is required prior to genetic testing, and the consent process includes explanations of the implications of testing, including the potential disclosure of secondary findings where applicable (Sasongko et al. 2015; Ministry of Health Malaysia, 2019). When such findings are identified, clinical laboratories commonly refer to international guidelines, particularly those issued by the American College of Medical Genetics and Genomics (ACMG), which provide recommendations for the reporting of selected actionable variants. However, despite the availability of ethical guidelines governing genetic testing in Malaysia, there remains a lack of a comprehensive and standardized national framework specifically addressing the reporting, communication, and long-term clinical management of secondary findings identified through genomic testing (Ministry of Health Malaysia, 2019; Nik Hassan et al. 2016).

Several challenges have been identified in the implementation of secondary findings in clinical practice. Differences in understanding among healthcare providers and patients may influence the effectiveness of result disclosure and subsequent clinical actions. Limited genomic literacy may affect patients' understanding of secondary findings, potentially influencing adherence to recommended follow-up actions such as cascade screening, surveillance, or preventive interventions (Setiawan et al. 2025; Rini et al. 2018). In addition, barriers such as limited access to specialist genetic services and variability in counselling practices may further affect the translation of genomic results into clinical benefit.

This highlights an important gap between the identification of secondary findings and their effective clinical utilisation. Even when such findings are reported, their overall benefit depends on how effectively they are communicated, understood, and acted upon by both healthcare providers and patients.

Therefore, this study will focus on the clinical management of secondary findings identified through Whole Exome Sequencing. By examining how these findings are handled following disclosure, this study aims to identify gaps in current practice and contribute evidence that may support the development of more structured approaches to improve patient care and the clinical utility of genomic testing in Malaysia.

1.3 OBJECTIVE OF RESEARCH

1.3.1 General Objective

To determine the prevalence and evaluate the current practices in the management of secondary findings identified through genetic testing at the Genetic Clinic of Hospital Kuala Lumpur (HKL) and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR).

1.3.2 Specific Objective

1. To determine the proportion of patients who opt in to receive secondary findings.
2. To determine the prevalence of secondary findings identified through WES.
3. To determine the genes associated with secondary findings identified through WES.
4. To describe the clinical management of secondary findings identified through WES.

1.4 RESEARCH QUESTIONS

The research questions are:

1. What proportion of patients undergoing Whole Exome Sequencing opt in to receive secondary findings?
2. What is the prevalence of secondary findings identified through Whole Exome Sequencing at Genetics Clinic, HKL and Genetics Clinic, Hospital TABTAR?
3. Which genes are most frequently associated with the secondary findings identified through WES?
4. What clinical follow-up actions are taken following the disclosure of secondary findings?

1.5 RESEARCH HYPOTHESIS

The hypothesis for this research are:

1. The proportion of patients who opt in to receive secondary findings at the Genetic Clinic of Hospital Kuala Lumpur (HKL) and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR) is expected to be within the range reported in established international studies.
2. The prevalence of clinically significant secondary findings identified through whole exome sequencing (WES) at HKL and Hospital TABTAR is expected to be within the range reported in previous studies.
3. Secondary findings involving cancer predisposition genes (BRCA1/BRCA2) and cardiovascular genes (LDLR, MYH7) are expected to represent a substantial proportion of the secondary findings identified among patients at HKL and Hospital TABTAR.
4. The identification and disclosure of secondary findings are expected to result in downstream clinical actions, including specialist referrals, clinical surveillance, genetic counselling, and cascade testing among patients and their families.

1.6 JUSTIFICATION OF THE STUDY

This research aims to provide a comprehensive audit of how secondary findings are currently managed in Malaysia, focusing on real clinical practices within a local genetics clinic. By identifying existing gaps and challenges, the study will contribute valuable evidence to support the development of clearer, standardized clinical framework tailored to Malaysia's unique healthcare context.

CHAPTER II

LITERATURE REVIEW

2.1 SECONDARY FINDINGS OF WHOLE EXOME SEQUENCING

Whole Exome Sequencing (WES) has become an important diagnostic tool in clinical genetics, particularly for individuals with suspected rare genetic disorders and undiagnosed diseases. By analysing the protein-coding regions of the genome, WES enables the identification of pathogenic variants associated with a wide range of Mendelian disorders (Yang et al. 2013). In addition to variants related to the primary indication for testing, WES may also identify genetic variants that are unrelated to the patient's presenting condition. These variants are known as secondary findings (SFs).

Secondary findings are generally defined as pathogenic or likely pathogenic variants identified during genomic sequencing that are unrelated to the original reason for testing but may have potential health implications for the individual. The increasing use of WES and Whole Genome Sequencing (WGS) has led to greater recognition of secondary findings as an important outcome of genomic testing. It has been estimated that approximately 1 to 4% of individuals undergoing clinical exome or genome sequencing harbour medically actionable secondary findings (Sapp et al. 2014).

Many secondary findings are associated with hereditary cancer syndromes, inherited cardiovascular disorders, and other genetic conditions for which preventive measures, surveillance programmes, or therapeutic interventions are available (Kalia et al. 2017; Miller et al. 2021). Early identification of these variants may allow individuals to undergo risk-reducing interventions and targeted clinical surveillance, which can facilitate earlier detection and management of disease. However, there is

still limited long-term evidence demonstrating a direct reduction in morbidity or mortality as a result of identifying secondary findings. Available studies have shown increased detection of at-risk individuals within families and subsequent implementation of preventive measures, although the long-term clinical impact remains uncertain. In addition, economic evaluations from the Clinical Sequencing Exploratory Research (CSER) consortium have reported that the healthcare costs associated with the management of secondary findings are generally feasible within clinical practice settings (Hart et al. 2019).

Despite their clinical utility, secondary findings present several challenges for healthcare professionals. The interpretation of genomic variants remains complex, particularly in the context of population-specific genetic diversity and evolving evidence regarding variant pathogenicity. Furthermore, advances in genomic medicine have raised important questions regarding uncertainty, risk prediction, and the interpretation of genetic information, particularly when findings are unrelated to the primary diagnostic indication (Han et al. 2021; Pyeritz 2021).

The prevalence of secondary findings varies considerably between studies, depending on factors such as population characteristics, sequencing platforms, variant classification criteria, and the version of the ACMG secondary findings list used. Most published data originate from North American, European, and East Asian populations, resulting in limited information regarding the prevalence and clinical management of secondary findings in Southeast Asian populations, including Malaysia (Tang et al. 2018). This knowledge gap highlights the need for local studies evaluating the occurrence and clinical implications of secondary findings in Malaysian healthcare settings.

2.2 ACMG RECOMMENDATIONS

The American College of Medical Genetics and Genomics (ACMG) plays a central role in guiding the reporting of secondary findings identified through clinical exome and genome sequencing. In 2013, the ACMG first recommended that laboratories actively search for and report pathogenic variants in a predefined list of medically actionable genes, regardless of the clinical indication for testing (Green et al. 2013).

The original ACMG recommendations established a minimum list of 56 genes associated with medically actionable conditions, including hereditary cancer syndromes, inherited cardiovascular disorders, and other serious genetic diseases for which preventive or therapeutic interventions are available, and recommended that pathogenic and likely pathogenic variants in these genes be reported regardless of the primary indication for testing. These recommendations were developed based on the principle that certain genetic findings may provide significant clinical benefit through early detection, risk stratification, and preventive intervention (Green et al. 2013).

The introduction of these recommendations generated considerable debate within the genetics community. Supporters argued that healthcare professionals have an ethical obligation to disclose medically actionable findings that may prevent morbidity and mortality, whereas critics raised concerns regarding patient autonomy, the right not to know, and the potential psychological burden associated with unsolicited genetic information (Burke et al. 2013; Wolf et al. 2015).

Since the initial publication of the ACMG secondary findings recommendations, the gene list has been periodically revised to reflect advances in genomic medicine, evolving evidence on disease penetrance, and improved understanding of variant pathogenicity and clinical actionability (Kalia et al. 2017; Miller et al. 2021). The current ACMG Secondary Findings (SF v3.3) list includes 84 genes associated with hereditary cancer syndromes, cardiovascular disorders, familial hypercholesterolaemia, and other medically actionable conditions for which established surveillance or preventive strategies are available.

The ACMG recommendations have been widely adopted internationally and are widely used as a key reference framework for clinical laboratories and healthcare professionals in the interpretation, reporting, and management of secondary findings (Green et al. 2013; Kalia et al. 2017; Miller et al. 2021). As genomic medicine continues to evolve, periodic updates to the gene list are expected to ensure that reporting practices remain aligned with current scientific evidence and clinical utility.

2.3 DISCLOSURE OF SECONDARY FINDINGS

The disclosure of secondary findings remains one of the most ethically challenging aspects of genomic medicine. Prior to testing, patients are typically informed about the possibility of identifying secondary findings and are provided with information regarding their options for receiving such results. This process is usually incorporated into pre-test genetic counselling and informed consent discussions (Saelaert et al. 2020).

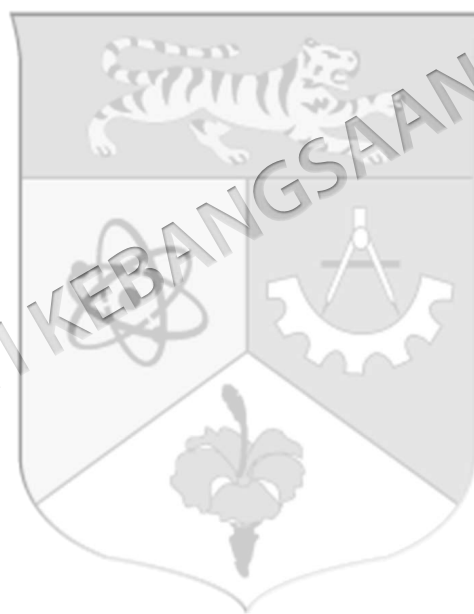
Patient autonomy is widely regarded as a fundamental ethical principle in the disclosure of secondary findings. Individuals should be provided with sufficient information to make informed decisions regarding whether they wish to receive medically actionable findings identified during genomic testing. Studies examining disclosure practices have demonstrated that respect for autonomy is frequently used to support patient choice and opt-out options for secondary findings (Saelaert et al. 2020; Middleton et al. 2016).

However, the principle of autonomy must often be balanced against beneficence and non-maleficence. Beneficence supports disclosure when findings may enable disease prevention or early intervention, whereas non-maleficence emphasises the avoidance of psychological distress, unnecessary anxiety, or inappropriate medical interventions (McGuire et al. 2013; Saelaert et al. 2020).

Qualitative studies involving healthcare professionals have shown that ethical decision-making regarding secondary findings often requires balancing competing ethical principles. Saelaert et al. (2020) reported that clinicians frequently considered autonomy, beneficence, and non-maleficence when making decisions about disclosure practices. The study also highlighted concerns related to patients' understanding of complex genomic information and the influence of genetic literacy on informed decision-making.

Patient perspectives regarding disclosure have generally been positive, with many individuals expressing willingness to receive medically actionable secondary findings, particularly when preventive or therapeutic measures are available (Berg et al. 2011; Middleton et al. 2016). Nevertheless, concerns regarding confidentiality, genetic discrimination, emotional burden, and family implications remain important considerations during disclosure discussions (Borry et al. 2008; Saelaert et al. 2020).

Effective communication is therefore essential during both pre-test and post-test counselling. Patients should be informed about the significance of identified variants, disease risks, available management strategies, and potential implications for family members. Transparent communication and shared decision-making may facilitate informed choices while supporting patient-centred care (McGuire et al. 2013).



2.4 FAMILY IMPLICATIONS OF SECONDARY FINDINGS

Secondary findings may have implications beyond the individual undergoing testing. Many conditions included in the ACMG secondary findings list follow autosomal dominant inheritance patterns, and therefore may place biological relatives at increased risk of developing the same condition (Green et al. 2013).

The identification of a pathogenic variant in one individual may prompt cascade testing among family members. Cascade testing refers to the systematic genetic evaluation of at-risk relatives to determine whether they carry the same pathogenic variant. This approach enables early identification of affected individuals and facilitates the implementation of surveillance or preventive measures before the onset of disease (Henneman et al. 2013).

Family communication represents an important aspect of secondary findings management. Patients may experience uncertainty regarding whether, when, and how genetic information should be shared with relatives. Ethical considerations include balancing patient confidentiality with the potential health benefits of informing at-risk family members (McGuire et al. 2013; Abad 2025).

Several studies have highlighted the importance of genetic counselling in supporting family communication and facilitating informed decision-making among relatives. Appropriate counselling may enhance patients' understanding of inheritance patterns, reproductive implications, and available options for cascade or familial testing (Saelaert et al. 2020; Henneman et al. 2013).

As genomic medicine becomes increasingly integrated into healthcare systems, the role of cascade testing is expected to become increasingly important in maximising the clinical benefits of secondary findings and improving population-level disease prevention (Henneman et al. 2013; Green et al. 2013).

2.5 CLINICAL MANAGEMENT AND FOLLOW-UP

The identification of a secondary finding often initiates a series of clinical management activities aimed at reducing disease risk and improving health outcomes. Management strategies depend on the specific gene involved, the associated condition, the patient's medical history, and relevant family history (Green et al. 2013).

Clinical management may include referral to specialist services, disease-specific surveillance programme, additional diagnostic investigations, pharmacological interventions, lifestyle modifications, or preventive surgical procedures. For example, individuals with pathogenic variants associated with hereditary cancer syndromes may require enhanced cancer surveillance, whereas those with inherited cardiovascular conditions may require cardiac evaluation and ongoing monitoring (Kalia et al. 2017; Ezekian et al. 2021).

The ACMG recommendations are based on the principle of medical actionability, whereby reported findings are expected to enable disease prevention, early detection, or treatment (Green et al. 2013). Consequently, the management of secondary findings often requires a multidisciplinary approach involving clinical geneticists, genetic counsellor, specialist physicians, and primary healthcare providers (McGuire et al. 2013).

Family screening represents an important component of the management of secondary findings. Identification of at-risk relatives may extend the benefits of genomic testing beyond the index patient and facilitate early intervention and preventive strategies within families (Henneman et al. 2013).

Long-term follow-up remains essential in genomic medicine, as recommendations for surveillance and management may evolve with emerging evidence. In addition, variant classifications may be re-evaluated as new data on gene-disease associations and pathogenicity become available. Ongoing review of genomic findings, together with coordinated multidisciplinary care, is therefore necessary to ensure optimal patient outcomes (Kalia et al. 2017; Miller et al. 2021).

2.6 KNOWLEDGE GAP IN THE MALAYSIAN CONTEXT

The reported prevalence of secondary findings identified through Whole Exome Sequencing (WES) varies considerably across studies. This variability is influenced by differences in study populations, sequencing methodologies, variant interpretation criteria, and the evolving versions of the ACMG secondary findings list (Green et al. 2013; Kalia et al. 2017; Miller et al. 2021).

Early studies following the implementation of the ACMG recommendations reported that approximately 1 to 4% of individuals undergoing clinical exome or genome sequencing harbour medically actionable secondary findings, depending on the cohort and variant interpretation criteria applied (Dorschner et al. 2013; Yang et al. 2014).

Comparisons across studies are further complicated by differences in sequencing platforms, variant classification frameworks, and population characteristics, which may influence the detection and reporting of secondary findings (Sapp et al. 2021).

More recent studies have demonstrated that the prevalence of medically actionable secondary findings may vary across populations. Studies in East Asian cohorts, including Korean genomic datasets, have reported prevalence estimates broadly comparable to those observed in Western populations, although some differences in variant distribution and allele frequencies have been observed, highlighting the importance of population-specific genomic data. Overall, reported prevalence across diverse populations ranges from approximately 1% to 4%, depending on the ACMG gene list version, sequencing approach, and variant interpretation criteria applied (Dorschner et al. 2013; Yang et al. 2014).

The prevalence of secondary findings may also increase as updates to the American College of Medical Genetics and Genomics (ACMG) recommendations introduce additional clinically actionable genes. Progressive expansion of the ACMG secondary findings list over time has increased the number of reportable genes, thereby enhancing the likelihood of identifying medically actionable variants during genomic testing (Green et al. 2013; Kalia et al. 2017; Miller et al. 2021).

However, there are currently no universally established guidelines mandating systematic reanalysis of previously reported or historical genomic data following updates to the ACMG secondary findings list. As such, re-evaluation of older genomic data is often dependent on institutional policies and clinical practice settings rather than standardised international protocols.

Despite growing international evidence, data regarding secondary findings in Southeast Asian populations remain limited. Most published studies originate from North America, Europe, and East Asia, resulting in limited evidence regarding the prevalence and clinical management of secondary findings within Malaysian healthcare settings. Differences in genetic diversity, healthcare infrastructure, availability of genetic services, and clinical practice patterns may influence both detection and management of secondary findings in Malaysia.

Therefore, local studies are essential to establish population-specific prevalence estimates, evaluate clinical management practices, and support the development of evidence-based genomic medicine in Malaysia.

2.7 RATIONALE FOR THE PRESENT STUDY

Whole exome sequencing (WES) has increasingly been integrated into clinical practice, leading to the identification of secondary findings. International studies have reported that medically actionable secondary findings occur in approximately 1 to 4% of individuals undergoing genomic sequencing, depending on study population, sequencing methodology, and variant interpretation criteria (Dorschner et al. 2013; Yang et al. 2014). Furthermore, numerous studies have highlighted the potential clinical benefits of identifying secondary findings, including opportunities for disease prevention, early diagnosis, and risk-reducing interventions (Green et al. 2013).

Despite the expanding body of international literature, there remains limited evidence regarding the prevalence and clinical management of secondary findings in Malaysia. Most published studies have been conducted in Western and East Asian populations, which may not accurately reflect the genetic diversity and healthcare context of the Malaysian population. In addition, variations in healthcare

infrastructure, availability of genetic counselling services, and clinical follow-up practices may influence the management of secondary findings across different settings.

Current literature has primarily focused on ethical considerations, reporting practices, and prevalence of secondary findings. Comparatively fewer studies have evaluated the downstream clinical management of individuals identified with secondary findings, including specialist referrals, cascade testing among family members, the implementation of surveillance strategies, and long-term follow-up. Such information is essential for assessing the real-world impact of genomic testing and determining whether the identification of secondary findings translates into meaningful clinical action.

To date, there is limited published local data describing the prevalence and management of secondary findings identified through WES within Malaysian clinical genetics services. Therefore, this study aims to evaluate the prevalence and clinical management of secondary findings identified through WES among patients from Hospital Kuala Lumpur (HKL) and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR). The findings are expected to contribute local evidence that may support the development of clinical guidelines, strengthen genetic counselling practices, and improve the integration of genomic medicine within the Malaysian healthcare system.

CHAPTER III

METHODOLOGY

3.1 STUDY SETTING

This study was conducted at two tertiary clinical genetics centres in Malaysia, namely the Genetics Clinic, Hospital Kuala Lumpur (HKL) and the Genetics Clinic, Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR). These centres provide specialised clinical genetic services, including Whole Exome Sequencing (WES) for patients with suspected genetic disorders.

3.2 STUDY DESIGN

This study employed a retrospective descriptive study design. Medical records, genetic counselling notes, and genetic testing reports of patients who underwent Whole Exome Sequencing (WES) at the participating centres were reviewed.

The study involved a retrospective review of WES reports issued between January 2021 and March 2026, with the aim of determining the prevalence of secondary findings and describing the clinical management following their disclosure.

As this study involved review of existing medical records, no direct patient contact or intervention was performed.

3.3 STUDY POPULATION

The required sample size was estimated based on an expected prevalence of approximately 3% for secondary findings (Niguidula et al., 2018), with a 95% confidence level and a 1% margin of error, using the standard formula for sample size estimation in prevalence studies. A 1% margin of error was selected to provide greater precision in estimating the prevalence of secondary findings, given the relatively low expected prevalence of approximately 3%. The expected prevalence (P) was set at 3%, while the Z value corresponding to a 95% confidence level was 1.96. The calculation (Figure 3.1) estimated a minimum required sample size of 1,119 patients. However, during the study period from January 2021 to March 2026, only 882 patients underwent Whole Exome Sequencing (WES) at Hospital Kuala Lumpur (HKL) and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, UKM (Hospital TABTAR). Therefore, convenience sampling of available records was employed, whereby all eligible records available during the study period were included in the study, resulting in a final available sample of 882 patients.

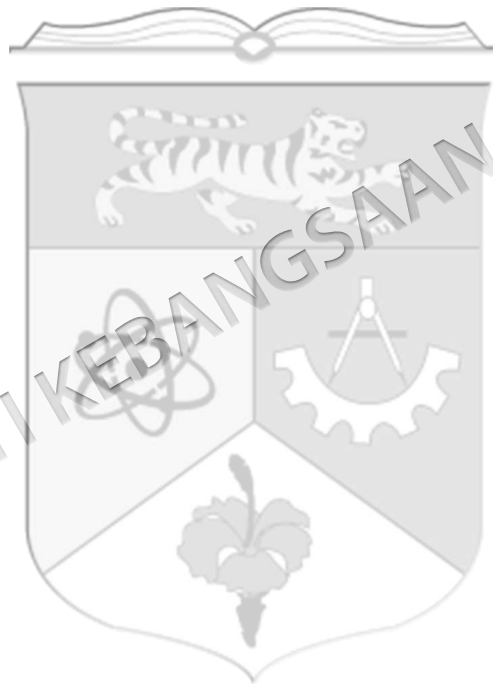
Of these 882 patients, 92 declined disclosure of secondary findings and were excluded from further screening. The remaining 790 patients constituted the cohort screened for secondary findings. Among these, 33 patients were identified as having secondary findings. Six patients were subsequently excluded because their clinical management was conducted outside the study centres ($n = 3$) or their medical records were unavailable at the time of data collection ($n = 3$). Therefore, 27 patients with secondary findings were included in the final analysis. The overall study flow is illustrated in Figure 3.2.

$$n = \frac{Z^2 \times p(1 - p)}{E^2}$$

$$n = \frac{(1.96)^2 \times 0.03 \times (1 - 0.03)}{(0.01)^2}$$

$$n = \frac{3.8416 \times 0.03 \times 0.97}{0.0001} = \frac{0.1119}{0.0001} = 1,119$$

Figure 3.1 Sample size calculation



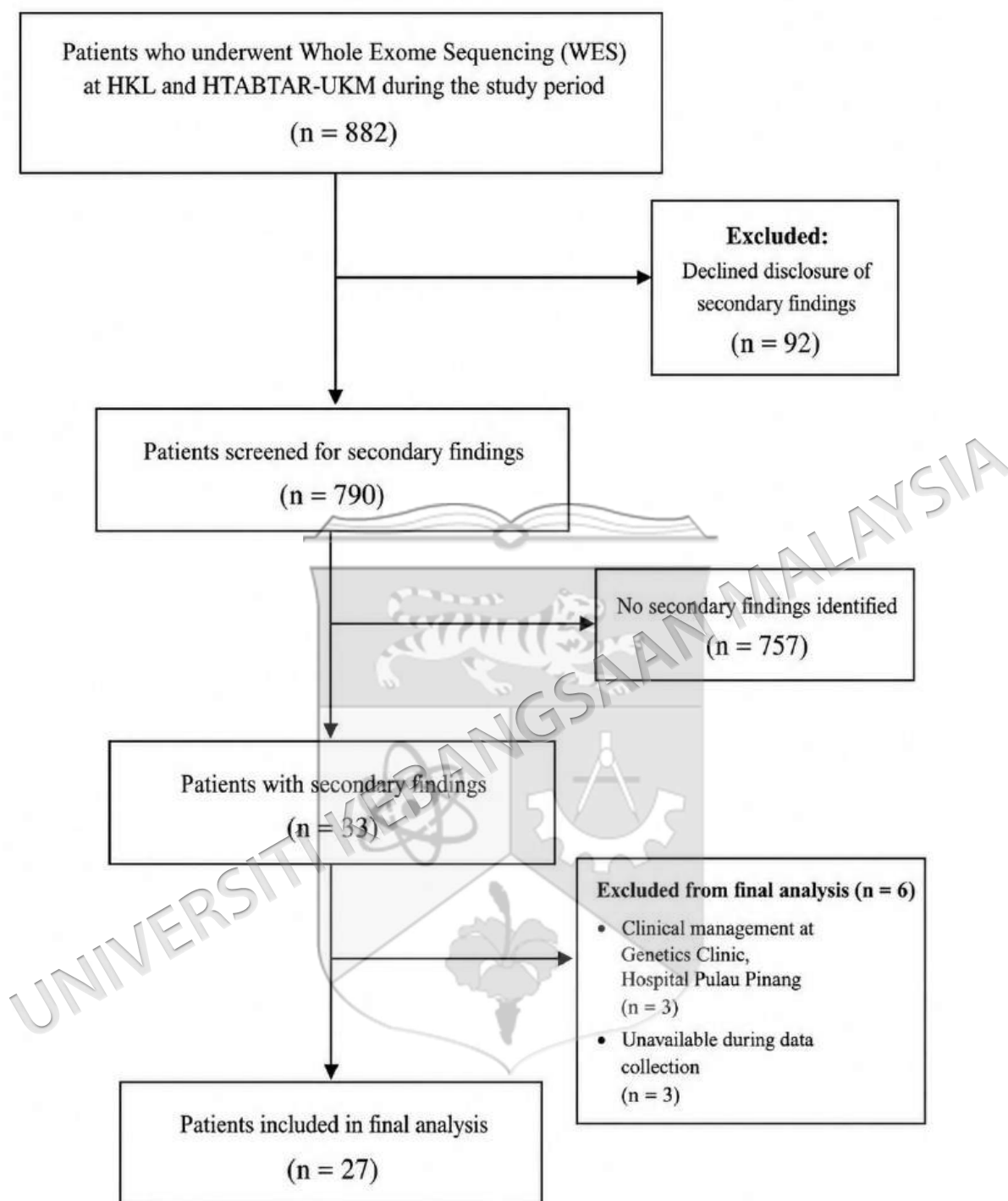


Figure 3.2 Flow diagram of the study population showing the selection of patients with secondary findings included in the final analysis

During the pre-test counselling process, patients and/or their parents or guardians were informed about the possibility of identifying secondary findings through WES and were given the option to decline the disclosure of such findings. For patients who declined to receive secondary findings, this preference was documented during the WES test ordering process. When the WES test was subsequently ordered, the option for reporting secondary findings was not selected. Upon completion of WES, no secondary findings were reported in the relevant section of the WES report. Instead, the report indicated that the patient had declined the disclosure of secondary findings and advised the treating clinician to refer to the relevant healthcare provider for further management. Therefore, patients who had documented refusal of secondary findings were identified from the WES test request and corresponding WES reports and were excluded from the screening for secondary findings in this study.

3.3.1 Inclusion Criteria

The inclusion criteria were:

1. Patients who underwent genetic testing using Whole Exome Sequencing (WES).
2. Patients with available genetic testing reports that included information regarding secondary findings.
3. Patients with complete clinical records, including counselling documentation and follow-up management records.

3.3.2 Exclusion Criteria

The exclusion criteria were:

1. Patients with incomplete or missing clinical records, including cases where genetic results had not yet been disclosed (post-test counselling not completed) or where essential clinical documentation was unavailable at the time of analysis.
2. Cases in which genetic testing was performed solely for research purposes without clinical follow-up.
3. Cases involving genetic variants that were not included in the American College of Medical Genetics and Genomics (ACMG) Secondary Findings (SF) v3.3-gene list.

3.4 STUDY VARIABLES

The variables in this study included demographic, clinical, and genetic-related parameters.

Demographic variables included age, sex, and ethnicity. Clinical variables included indication for Whole Exome Sequencing (WES) testing and clinical management following the identification of secondary findings.

Genetic variables included genes associated with secondary findings and variant classification according to the American College of Medical Genetics v3.3.

Outcome variables included the presence of secondary findings and the associated clinical management outcomes. These included specialist referrals, surveillance strategies, cascade testing, and follow-up arrangements following the identification of secondary findings.

3.5 DATA COLLECTION

Data were collected through a retrospective review of medical records, genetic counselling notes, and genetic testing reports from both participating centers. A structured data collection form was used to ensure consistency during data extraction.

The information collected included demographic characteristics such as age, sex, and ethnicity, as well as information related to genetic testing, identified secondary findings, their clinical management, and patient outcomes. All patient identifiers were removed prior to data analysis to maintain confidentiality.

3.6 DATA ANALYSIS

Data analysis was performed using descriptive statistical methods. All data were summarized and presented in a structured format according to the study objectives.

Continuous variables such as age were described using mean and standard deviation if normally distributed, or median and interquartile range if not normally distributed. Categorical variables were summarised using frequencies and percentages.

The prevalence of secondary findings identified through Whole Exome Sequencing (WES) was determined and expressed as a percentage of the total study population.

In addition, genes associated with secondary findings were summarised and presented in tabulated form. Clinical management following the identification of secondary findings, including specialist referrals, surveillance measures, cascade testing, and follow-up arrangements, was analysed and presented descriptively.

All analyses were conducted based on structured data extraction in accordance with the study design and supervisory guidance. Data were organised and managed using Microsoft Excel, and descriptive analyses, including frequencies, percentages, means, and standard deviations, were performed as appropriate to summarise the study findings.

3.7 ETHICAL CONSIDERATIONS

Ethical approval for this study was obtained from the Research Ethics Committee of Universiti Kebangsaan Malaysia (JEPUKM) prior to the commencement of data collection. In addition, approval was obtained through the National Medical Research Register (NMRR) to allow access to patient data from Hospital Kuala Lumpur (HKL).

As this study involved a retrospective review of existing medical records, no direct interaction with patients was required. All data were obtained from medical records, genetic counselling notes, and genetic testing reports.

Patient confidentiality was strictly maintained throughout the study. All personal identifiers were removed prior to data analysis to ensure anonymity. Each participant was assigned a unique study code, and no identifying information was included in the final data set or analysis.

Data extracted for this study were printed for the purpose of structured data verification and manual extraction. All printed documents were securely stored by the principal investigator in a locked and restricted-access environment. These documents were accessible only to the research team and were used solely for data verification and analysis purposes. Upon completion of the study, all hard copy documents will be securely disposed of in accordance with institutional data protection and ethical guidelines.

CHAPTER IV

RESULTS

4.1 SECONDARY FINDINGS

During the study period, a total of 882 patients underwent Whole Exome Sequencing (WES). Of these, 92 patients (10.43%) chose not to receive secondary findings disclosure and were therefore excluded from further analysis. The remaining 790 patients (89.57%) consented to secondary findings reporting and formed the eligible study cohort for analysis.

From this cohort, 33 patients (4.18%) were identified with secondary findings. Following exclusion of six patients (three were managed at a non-study site, two had records that were inaccessible due to retention under a separate research protocol, and one had no documented result disclosure as the patient did not attend the scheduled disclosure appointment.), 27 patients were included in the final analysis.

Among these 27 patients, a total of 28 secondary findings were identified, as one patient harboured pathogenic variants in two clinically actionable genes (GLA and LDLR). The prevalence of secondary findings among the study cohort was 4.18% (33/790), representing patients who opted in for secondary findings reporting.

4.2 PATIENT DEMOGRAPHICS

A total of 27 patients were included in the clinical management analysis. The cohort consisted of 14 female patients (51.85%) and 13 male patients (48.15%), demonstrating a relatively balanced sex distribution. The majority of patients were Malay (70.37%, $n = 19$), followed by Chinese (18.52%, $n = 5$), while Indian, Orang Asli, and Melanau patients each accounted for 3.70% ($n = 1$). The age of patients at the time of testing ranged from 0.25 to 37 years, with a mean (SD) age of 9.56 (9.31) years. Children aged 1–12 years constituted the largest age group (51.85%, $n = 14$), followed by infants aged below one year and adolescents aged 13–18 years, each accounting for 18.52% ($n = 5$). Adults aged over 18 years comprised 11.11% ($n = 3$) of the cohort. The demographic characteristics of the study participants are presented in Table 4.1.

Table 4.1 Demographic Characteristics of Study Participants

Demographic characteristic	Frequency (n)	Percentage (%)
Sex		
Male	13	48.15
Female	14	51.85
Ethnicity		
Malay	19	70.37
Chinese	5	18.52
Indian	1	3.70
Orang Asli	1	3.70
Melanau	1	3.70
Age Group		
<1 year	5	18.52
1-12 years	14	51.85
13-18 years	5	18.52
>18 years	3	11.11
Total	27	100.00

Overall, the study population was predominantly paediatrics, with patients aged below 18 years comprising the majority of the cohort. Malay patients constituted the largest ethnic group, while the distribution of male and female patients was relatively balanced.

4.3 TESTING INFORMATION

4.3.1 Overview of Genetic Testing

All patients included in this study underwent Whole Exome Sequencing (WES) as the primary diagnostic test. This reflects the use of WES as a first-line genomic tool for the evaluation of heterogeneous paediatric and multisystem disorders within the study cohort.

4.3.2 Clinical Indications for Testing

The clinical indications for Whole Exome Sequencing (WES) were diverse. The majority of patients presented with neurodevelopmental disorders, syndromic features, congenital anomalies, epilepsy-related conditions, and suspected metabolic or genetic disorders.

In the clinical setting, the selection of genetic testing modality was influenced by both clinical indication and resource availability. Patients with suspected chromosomal abnormalities or structural genetic disorders were often initially evaluated using conventional cytogenetic testing such as karyotyping, particularly in cases where cost constraints were present. In selected patients, WES was subsequently performed when more comprehensive genomic analysis was indicated or when prior investigations were non-diagnostic.

In addition, several patients underwent WES for specific suspected monogenic syndromes, including Treacher Collins syndrome, Stickler syndrome, Dravet syndrome, MELAS syndrome, and other clinically suspected genetic conditions.

Overall, the cohort reflected a wide spectrum of clinical presentations and diagnostic pathways, consistent with real-world genomic practice in a resource-variable healthcare setting.

4.3.3 Diagnostic Outcomes

The overall diagnostic outcomes from WES were classified into pathogenic/likely pathogenic (positive), variant of uncertain significance (VUS), and negative results.

Table 4.2 Diagnostic Outcomes of Whole Exome Sequencing

Outcome	Frequency (n)	Percentage (%)
Pathogenic / Likely Pathogenic	6	22.22
Variant of Uncertain Significance (VUS)	8	29.63
Negative	13	48.15
Total	27	100

The largest proportion of patients had negative results (48.15%), followed by VUS (29.63%), while approximately 22.22% of patients had pathogenic or likely pathogenic variants.

4.3.4 Spectrum of Suspected Genetic Disorders (Indications for WES)

The primary indications for Whole Exome Sequencing (WES) in this cohort were heterogeneous and involved multiple clinical categories. Neurodevelopmental and neurological disorders constituted the largest group ($n = 12$, 44.44%), including epilepsy syndromes, intellectual disability, developmental delay, autism spectrum disorders, and suspected neurodevelopmental conditions such as Dravet syndrome, SMC1A-related early infantile epileptic encephalopathy, and MELAS syndrome.

Craniofacial and skeletal disorders accounted for 7 cases ($n = 7$, 25.93%), including Treacher Collins syndrome, Stickler syndrome, CODAS syndrome, Blepharophimosis-ptosis syndrome, multiple exostoses, and other craniofacial or skeletal dysmorphism-related indications.

Cardiovascular or suspected inherited cardiac-related conditions comprised 5 cases ($n = 5$, 18.52%), including suspected familial cardiac disorders and hypercholesterolaemia-related indications.

Chromosomal or suspected structural genetic disorders were reported in 2 patients ($n = 2$, 7.41%), including chromosome 10q22.3–q23.2 deletion syndrome and suspected submicroscopic chromosomal abnormalities. A single case ($n = 1$, 3.70%) was classified as a metabolic or mitochondrial disorder, represented by suspected MELAS syndrome.

All 27 cases were included and classified according to the primary clinical indication documented at the time of WES referral.

4.3.5 Results of WES Analysis (Genetic Findings)

The genetic findings demonstrated a heterogeneous spectrum, comprising pathogenic or likely pathogenic variants, variants of uncertain significance (VUS), and cases with no clinically actionable findings.

Pathogenic or likely pathogenic variants were identified in six patients (22.22%). These findings were considered clinically significant based on established disease associations and potential implications for clinical management and surveillance. The pathogenic findings included SMC1A-related early infantile epileptic encephalopathy (EIEE), Mowat–Wilson syndrome (ZEB2-related), Treacher Collins syndrome (TCOF1), chromosome 10q22.3–q23.2 deletion syndrome, multiple exostoses type 1, and MELAS syndrome (MT-TL1). These variants represented a spectrum of neurodevelopmental, craniofacial, skeletal, and mitochondrial disorders with recognised clinical relevance and potential impact on patient care.

Variants of uncertain significance (VUS) were identified in eight patients (29.63%). These variants were detected in genes associated with suspected clinical conditions; however, current evidence was insufficient to support pathogenic classification. The VUS findings involved genes related to suspected Treacher Collins syndrome (TCOF1), Dravet syndrome (SCN1A), pseudohypoaldosteronism type IB1,

Stickler syndrome spectrum disorders, BRUCK syndrome 2, blepharophimosis-ptosis syndrome, CODAS syndrome, and FDXR-related variants. These findings highlight the ongoing challenges in variant interpretation and the need for cautious clinical correlation in genomic diagnostics.

The remaining 13 patients (48.15%) had no pathogenic or likely pathogenic secondary findings detected on WES. Although several patients in this group presented with clinical features suggestive of genetic disorders, no actionable variants meeting the criteria for secondary findings were identified.

Overall, the distribution of WES findings demonstrates that nearly half of the cohort had negative results, while approximately one-fifth had clinically actionable pathogenic variants, with the remainder classified as VUS. This reflects the complexity of genomic interpretation and reinforces the importance of integrating molecular findings with clinical evaluation in the context of secondary findings reporting.

4.3.6 Family History and Cascade Testing

Of the 27 patients analysed, 17 (62.96%) had a relevant family history of genetic or complex diseases, while 10 (37.04%) had no relevant family history. Among those with positive family history ($n = 17$), 7 (41.18%) had a history of hereditary cancer syndromes, including colorectal, breast, ovarian, uterine, and lung cancers. A further 6 (35.29%) reported a family history of cardiovascular or metabolic disorders, including hypercholesterolaemia, heart disease, tachycardia, and stroke. The remaining 4 (23.53%) had a family history of neurological or other genetic conditions.

These findings demonstrate the heterogeneity of familial disease patterns among individuals undergoing whole exome sequencing and highlight the potential utility of cascade testing in at-risk families.

4.4 ANALYSIS OF SECONDARY FINDINGS

4.4.1 Variant Classification of Secondary Findings

Of the 28 secondary findings identified, 13 (46.43%) were classified as pathogenic, while 15 (53.57%) were classified as likely pathogenic (Table 4.5).

Table 4.3 Classification of Secondary Findings Identified through Whole Exome Sequencing

Outcome	Frequency (n)	Percentage (%)
Pathogenic	13	46.43
Likely Pathogenic	15	53.57
Total	28	100

4.4.2 Genes Associated with Secondary Findings

A total of 17 different genes were identified among the secondary findings. The most frequently identified gene was LDLR (n = 4), followed by MYH7, TTN, and BRCA2 (n = 3 each). BRCA1 and GLA were each identified in two patients. The remaining 11 genes, namely MYBPC3, DSC2, KCNQ1, KCNH2, MLH1, PMS2, BMPR1A, RET, PTEN, RYR1, and SDHC, were each identified in one patient.

Table 4.4 Secondary Findings by Disease Category and Associated Genes

Disease Category	Gene	Frequency (n)	Disease Association
Cardiovascular Disorders (n = 14, 50.0%)	LDLR	4	Familial hypercholesterolemia
	MYH7	3	Cardiomyopathy
	TTN	3	Cardiomyopathy
	MYBPC3	1	Hypertrophic cardiomyopathy
	DSC2	1	Arrhythmogenic right ventricular dysplasia
	KCNQ1	1	Long QT syndrome 1
	KCNH2	1	Long QT syndrome 2
Hereditary Cancer Syndromes (n = 10, 35.71%)	BRCA2	3	Hereditary breast and ovarian cancer
	BRCA1	2	Hereditary breast and ovarian cancer
	MLH1	1	Lynch syndrome

Other Inherited Disorders (n = 4, 14.29%)	PMS2	1	Lynch syndrome
	BMPR1A	1	Juvenile polyposis syndrome
	RET	1	Multiple endocrine neoplasia type 2
	PTEN	1	Cowden syndrome
	GLA	2	Fabry disease
	RYR1	1	Malignant hyperthermia susceptibility
	SDHC	1	Paraganglioma syndrome

4.4.3 Disease Categories Associated with Secondary Findings

The identified secondary findings were grouped into three major disease categories: cardiovascular disorders, hereditary cancer syndromes, and other inherited disorders.

Cardiovascular disorders represented the largest category, accounting for 14 of 28 secondary findings (50.0%). This category included genes associated with cardiomyopathy, inherited arrhythmia syndromes, and familial hypercholesterolaemia, namely LDLR, MYH7, TTN, MYBPC3, DSC2, KCNQ1, and KCNH2.

Hereditary cancer syndromes accounted for 10 secondary findings (35.71%). The genes identified included BRCA1, BRCA2, MLH1, PMS2, BMPR1A, RET, and PTEN, which are associated with hereditary breast and ovarian cancer syndrome, Lynch syndrome, juvenile polyposis syndrome, and multiple endocrine neoplasia type 2.

The remaining three findings (14.29%) were associated with other inherited disorders, comprising GLA, RYR1, and SDHC, which are linked to Fabry disease, malignant hyperthermia susceptibility, and hereditary paraganglioma syndrome, respectively.

4.4.4 Secondary Findings Disclosure

Secondary findings were disclosed to all 27 patients included in the analysis (100%). In one case, an initial result disclosure was conducted via telephone, however, the written report was subsequently formally communicated during a follow-up in-person prenatal counselling session attended by the patient's mother. Final documented disclosure was therefore completed during this visit.

Table 4.5 Disclosure Status of Secondary Findings

Disclosure Status	Frequency (n)	Percentage (%)
Disclosed	27	100
Total	27	100

4.4.5 Multiple Secondary Findings in a Single Patient

One patient was found to have two clinically actionable secondary findings involving the GLA and LDLR genes. These findings are associated with Fabry disease and Familial hypercholesterolemia, respectively. Both conditions have established screening and management recommendations, showing that genomic testing can identify more than one important health risk in a single individual.

4.5 MANAGEMENT OF SECONDARY FINDINGS

Management outcomes following identification of secondary findings were evaluated for all 27 patients. Data were categorized into referral patterns, cascade testing, genetic counselling, and clinical surveillance.

As shown in Table 4.8, 14 of 27 patients (51.85%) were referred to relevant clinical services following the identification of secondary findings. Cardiology was the most frequent referral service, accounting for 12 of the 14 referrals (85.71%), reflecting the predominance of cardiovascular-related secondary findings in the study cohort. The remaining two patients (14.29%) were referred to endocrinology for further evaluation of endocrine-related secondary findings.

Table 4.6 Referral to Clinical Services based on Secondary Findings

Referral Status	Frequency (n)	Percentage (%)
Referral made	14	51.85
No Referral	13	48.15
Total	27	100

The remaining 13 patients (48.15%) did not proceed with referral to a clinical service at the time of data collection. The reasons varied according to the nature of the secondary finding and the individual circumstances of the patients. Some patients or families were not ready to proceed with further clinical evaluation and preferred to defer referral. For patients with hereditary cancer predisposition findings, referral or cancer-related surveillance was deferred when the patient had not yet reached the age at which the relevant surveillance would be clinically indicated. In these cases, immediate referral was not considered necessary at the time of data collection, with further surveillance to be considered when the patient reached the appropriate age or when clinically indicated. In one patient, referral was not pursued because the patient had passed away before further clinical evaluation could be undertaken. In other cases, parents or guardians preferred to arrange further assessment or management through private healthcare services rather than the study centres. These families therefore did not proceed with referral through the study centres, as they intended to seek the appropriate clinical evaluation independently.

Table 4.7 Cascade Testing

Cascade Testing Outcome	Frequency (n)	Percentage (%)
Offered to family members	27	100
Testing performed in relatives	9	33.33
Not performed	10	37.04
Pending	8	29.63
Total	27	100

Cascade testing was offered to all 27 families (100%). Cascade testing uptake among relatives was variable. Of the families offered testing, nine (33.3%) proceeded with cascade testing, while 10 (37.04%) did not undergo testing. The reasons for non-performance included lack of interest or readiness to proceed at the time of counselling, with some relatives expressing a preference to defer decision-making to a later appointment. However, several of these individuals were subsequently lost to follow-up or did not re-attend for further discussion despite initial agreement to reconsider testing.

In addition, some cases of non-performance were attributed to initial expectations that targeted testing could be performed locally, however, it was later determined that the specific gene testing was no longer available locally, resulting in delays while awaiting alternative laboratory arrangements.

A further eight families (29.6%) remained pending testing at the time of analysis, primarily due to ongoing financial constraints, awaiting external financial assistance, or a decision to defer testing until the next clinical visit following counselling.

Table 4.8 Genetic Counselling

Counselling Status	Frequency (n)	Percentage (%)
Provided	27	100
Counsellor	Frequency (n)	Percentage (%)
Clinical Geneticist	23	85.19
Genetic counsellor + Clinical Geneticist	4	14.81

Genetic counselling was provided in all 27 cases included in the analysis (100%). In 23 cases, counselling sessions were conducted solely by clinical geneticists, while in the remaining 4 cases, counselling was jointly delivered by a clinical geneticist and a genetic counsellor. In all sessions, counselling was tailored to the individual clinical indications and genetic findings, with discussion focusing on interpretation of results, inheritance patterns, recurrence risks, and implications for family members. Where appropriate, information regarding cascade testing and recommendations for clinical follow-up was also provided.

Table 4.9 Clinical Surveillance / Preventive Actions

Surveillance type	Frequency (n)	Percentage (%)
Cardiac screening	12	44.44
Endocrine surveillance	2	7.40
No surveillance initiated	13	48.15
Total	27	100

Clinical surveillance or preventive interventions were implemented in 14 of 27 patients (51.85%). Cardiac screening, primarily in the form of echocardiography or cardiology assessment, was the most commonly performed intervention (12/27, 44.44%), while two patients (7.40%) were referred to endocrinology for further evaluation and management related to their secondary findings.

In contrast, 13 patients (48.15%) did not undergo any clinical surveillance at the time of data collection. This was attributed to a combination of factors, including loss to follow-up, patient or parental decision to defer further management after genetic counselling, age-related ineligibility for immediate intervention in cases involving adult-onset conditions, and socioeconomic or logistical barriers affecting attendance and continuation of care. In some cases, parents of paediatric patients with secondary findings preferred to defer cascade testing for themselves, as they considered themselves healthy and did not perceive an immediate need for genetic testing.

4.6 OUTCOMES

Following disclosure of genetic results and referral to relevant clinical services, patient outcomes demonstrated a wide spectrum of follow-up patterns. These outcomes were influenced by clinical urgency, patient age, family engagement, as well as socioeconomic and logistical factors.

Overall, five outcome categories were identified: (i) completed follow-up, (ii) pending follow-up, (iii) defaulted follow-up, (iv) no active referral indicated due to clinical or age-related considerations, and (v) death prior to completion of follow-up.

Table 4.13 summarises the distribution of outcomes among the 27 patients included in this study.

Table 4.10 Clinical Follow-up Outcomes Following Identification of Secondary Findings

Outcome category	Frequency (n)	Percentage (%)
Completed follow-up / Attended follow-up	10	37.04
Pending Follow-up	3	11.11
Defaulted follow-up	8	29.63
No referral / not yet clinically indicated	5	18.52
Deceased	1	3.70
Total	27	100

A total of 10 patients (37.04%) demonstrated compliant follow-up following genetic clinic referral. These patients adhered to recommended clinical management, including attendance at relevant specialty clinics such as cardiology and endocrinology, and completion of indicated investigations such as echocardiography. In most cases, the results of these assessments were within normal limits, and ongoing surveillance was planned where appropriate.

Three patients (11.11%) were classified as having pending follow-up. This group included individuals who had either initiated follow-up or agreed to further clinical evaluation but had not yet completed scheduled appointments or investigations at the time of data analysis.

Defaulted follow-up was observed in 8 patients (29.63%). This included patients who defaulted scheduled appointments, were lost to follow-up after genetic result disclosure, or were unable to continue care due to socioeconomic limitations, lack of engagement, or patient-related factors affecting attendance and continuity of care.

In 5 patients (18.52%), no follow-up was indicated at the time of analysis. This was mainly due to clinical judgement or age-related considerations, where surveillance was deferred until an appropriate age, or in cases where patients were already under established care in another specialty prior to genetic clinic involvement.

One patient (3.70%) died at 6 weeks of age prior to completion of follow-up, resulting in absence of post-referral outcome data.

4.7 SUMMARY OF KEY FINDINGS

Overall, only a minority of patients demonstrated full compliance with recommended follow-up following genetic clinic referral. The largest proportions of the cohort were either lost to follow-up or had incomplete management pathways, including pending review and cases where no follow-up was indicated based on clinical or age-related considerations.

These findings highlight the variability in post-diagnostic care pathways after identification of secondary findings, reflecting challenges in ensuring continuity of care beyond the initial genetic evaluation. Contributing factors likely include patient-related barriers, socioeconomic constraints, variable readiness for further clinical intervention, and differences in perceived clinical urgency among families and healthcare providers.

Collectively, these results underscore the challenges in translating genomic findings into sustained and coordinated clinical management, particularly in paediatric populations and in conditions requiring long-term or multisystem surveillance.

CHAPTER V

DISCUSSION

5.1 OVERVIEW OF STUDY FINDINGS

This study evaluated the management of secondary findings (SF) identified through Whole Exome Sequencing (WES) in a cohort of 27 patients. A total of 28 secondary findings were detected during the study period, representing clinically actionable variants identified incidentally in genomic testing. Notably, the presence of 28 secondary findings in 27 patients indicates that at least one individual harboured more than one secondary finding, reflecting the possibility of multiple clinically relevant genomic variants within a single patient in comprehensive sequencing analyses (Manickam et al. 2021; Posey et al. 2017).

The majority of secondary findings were classified as pathogenic or likely pathogenic variants, with 46.43% classified as pathogenic and 53.57% as likely pathogenic. Cardiovascular related genes represented the most common disease category, followed by hereditary cancer syndromes and other inherited disorders. Overall, cardiovascular disorders accounted for 50.0% of secondary findings, followed by hereditary cancer syndromes (35.71%) and other inherited conditions (14.29%).

In terms of clinical management, 51.85% of patients were referred to relevant clinical specialties, most commonly cardiology (75%). Cascade testing was offered to all 27 patients. Uptake of cascade testing among relatives remained limited, with 33.33% completing testing. Among those who did not complete testing, 37.04% represented individuals who were not keen to proceed despite repeated counselling and deferred decision-making at follow-up visits, while 29.63% remained pending due to ongoing factors such as awaiting scheduled appointments, financial assistance, or availability of local laboratory testing services. Genetic counselling was provided in all 27 cases (100%), with most sessions conducted by clinical geneticists.

5.2 INTERPRETATION OF FINDINGS

The distribution of secondary findings observed in this study is consistent with the American College of Medical Genetics and Genomics (ACMG) recommendations for reporting secondary findings, which prioritise genes associated with highly actionable conditions such as cardiomyopathies, inherited arrhythmia syndromes, familial hypercholesterolaemia, and hereditary cancer syndromes (Green et al. 2013; Miller et al. 2021). These genes are selected based on their clinical actionability, disease penetrance, and the availability of established surveillance or preventive strategies.

The predominance of cardiovascular-related genes such as TTN, MYH7, LDLR, MYBPC3, KCNQ1, and KCNH2 reflects the strong representation of cardiac conditions within actionable genomic findings. Notably, approximately 33 out of 84 genes in the ACMG secondary findings list are associated with cardiovascular diseases, highlighting the substantial proportion of cardiac-related conditions within clinically actionable variants. This is consistent with previous genomic implementation studies demonstrating that cardiovascular genes constitute a major proportion of secondary findings due to their well-characterised genotype–phenotype relationships and the availability of preventive interventions (Kalia et al. 2017; Miller et al. 2021).

Similarly, hereditary cancer genes including BRCA1, BRCA2, MLH1, PMS2, RET, and PTEN highlight the importance of cancer predisposition syndromes in secondary findings reporting. Notably, 28 out of 84 genes in the ACMG secondary findings list are associated with hereditary cancer syndromes, underscoring the substantial representation of cancer-related conditions among clinically actionable variants. These genes are clinically significant because early detection enables surveillance and risk-reducing interventions, reinforcing the preventive value of genomic testing beyond diagnostic purposes.

5.3 CLINICAL IMPLICATIONS

This study highlights several important clinical implications for genomic medicine.

First, secondary findings identified through WES are highly actionable and require multidisciplinary management involving cardiology, oncology, endocrinology, and other specialties depending on gene involvement. The predominance of cardiology referrals in this cohort reflects the high burden of cardiovascular-related actionable variants and aligns with previous genomic implementation studies reporting similar trends (Kalia et al. 2017; Miller et al. 2021). This reinforces the need for structured clinical pathways to ensure timely referral and coordinated care following genomic diagnosis.

Second, genetic counselling plays a critical role in supporting patient and family understanding of secondary findings. Although counselling was provided in the majority of cases, some patients defaulted follow-up or did not complete recommended surveillance. This highlights the need for more structured follow-up systems, improved communication strategies, and enhanced patient engagement, particularly in cases involving delayed or telephone-based disclosures.

Third, cascade testing remains an important component of genomic medicine. Although cascade testing was offered to all families in this study, uptake remained limited. Factors documented in the available clinical records that may have contributed to non-uptake included limited awareness among relatives, psychological readiness, financial constraints, and logistical barriers. This finding emphasises the need for improved family communication strategies and better access to subsidised genetic testing.

Finally, the identification of actionable variants in asymptomatic individuals supports the integration of genomic testing into routine clinical practice, particularly in paediatrics populations. Early identification of at-risk individuals provides opportunities for preventive intervention, surveillance, and long-term risk reduction, strengthening the role of genomic medicine in preventive healthcare (Green et al. 2013).

Overall, clinical management outcomes demonstrated that while most patients were appropriately referred and counselled, post-test implementation remained suboptimal, with gaps in follow-up adherence and cascade testing uptake. Clinical surveillance was initiated in more than half of patients, however, variability in follow-up highlights real-world challenges in translating genomic findings into sustained clinical action.

5.4 CHALLENGES IN MANAGEMENT OF SECONDARY FINDINGS

Several challenges were identified in the management of secondary findings in this cohort. Overall, 37.04% of patients demonstrated compliant follow-up with recommended surveillance, while 29.63% had no follow-up or defaulted from scheduled care. In addition, 11.11% of patients had pending follow-up at the time of analysis, 18.52% had no referral indicated due to clinical or age-related considerations, and one patient (3.70%) was deceased.

Suboptimal follow-up remains a key challenge, as a substantial proportion of patients either defaulted or did not re-engage with recommended clinical pathways after genetic result disclosure. Patient-related factors contributed to this, including perceptions that the identified genetic findings were non-modifiable and therefore not actionable, leading to reduced motivation for ongoing clinical follow-up or surveillance.

In some cases, patients or families also perceived a lack of immediate clinical benefit, particularly as many of the secondary findings represented incidental findings in otherwise asymptomatic individuals, such as pathogenic variants in cancer predisposition genes (e.g. BRCA1) identified in families without a prior history of malignancy. This may have further influenced engagement with long-term surveillance.

Socioeconomic constraints also played an important role, particularly the need for out-of-pocket payment for follow-up investigations and cascade testing, which limited access to recommended surveillance and family-based genetic testing. These financial barriers further affected continuity of care and contributed to delayed or absent clinical engagement.

System-related issues were also identified, including fragmented continuity of care and incomplete follow-up documentation, especially in cases where patients did not attend scheduled appointments after result disclosure. These findings highlight the need for improved tracking and coordination within genomic medicine services to ensure sustained follow-up.

Age-related factors further influenced management decisions, as some patients were not yet eligible for specific interventions. In these cases, clinical surveillance was appropriately deferred in accordance with established clinical judgement and guideline-based practice. However, this highlights the importance of structured long-term follow-up systems to ensure that these individuals are re-contacted when they reach the appropriate age for surveillance or intervention. This may be facilitated through a dedicated patient registry or tracking system within the clinical genetics service, with defined responsibility assigned to the managing clinical team or designated genetic service coordinator to ensure continuity of care and timely recall.

Overall, these findings highlight that the clinical utility of secondary findings is highly dependent not only on result identification, but also on effective communication, patient understanding, and continuity of follow-up within the healthcare system.

5.5 COMPARISON WITH EXISTING LITERATURE

The prevalence of secondary findings in this study (3.42%) is consistent with previously reported rates ranging from approximately 1% to 4% in exome sequencing cohorts, depending on gene lists and population characteristics (Kalia et al. 2017; Miller et al. 2021).

The observed distribution of cardiovascular and cancer-related genes aligns with ACMG secondary findings recommendations, which prioritise genes with high penetrance and established clinical actionability. Similar studies have reported TTN, LDLR, BRCA1, and BRCA2 as among the most frequently identified secondary findings (Miller et al. 2021; Green et al. 2013).

Cascade testing uptake in this study (33.33%) was lower compared to international reports, reflecting variability in healthcare systems and access to genetic services. Previous studies have shown that cascade testing uptake is influenced by multiple factors, including awareness of genetic risk, effectiveness of family communication, and socioeconomic barriers limiting access to genetic services (Henneman et al. 2013).

Similarly, follow-up compliance rates were lower than expected, aligning with previous studies highlighting challenges in translating genomic findings into sustained clinical action in real-world settings (Mitchell et al. 2024).

5.6 STRENGTHS AND LIMITATIONS OF THE STUDY

5.6.1 Strengths of the Study

This study has several strengths. First, it provides real-world evidence on the clinical management and outcomes of secondary findings identified through Whole Exome Sequencing (WES) within the Malaysian healthcare setting. Unlike studies that primarily focus on the prevalence or identification of secondary findings, this study examined the subsequent clinical management following disclosure, including genetic counselling, specialist referral, clinical surveillance, and cascade testing.

Second, the study utilised clinical data from established genetic services, allowing the findings to reflect actual clinical practice. The inclusion of patients from two genetic clinics also provides insight into the implementation of secondary findings management across different clinical settings within the local healthcare system.

Third, the study assessed multiple components of post-disclosure management. These included referral to relevant specialties, implementation of clinical surveillance, provision of genetic counselling, and cascade testing among at-risk relatives. This comprehensive assessment allowed the study to identify both areas of successful clinical implementation and gaps in the management pathway.

Fourth, the use of clinical records and genetic counselling documentation enabled the assessment of management outcomes based on documented clinical actions. This provided an objective assessment of the implementation of recommended management following the identification and disclosure of secondary findings.

Finally, this study contributes to the limited evidence on the real-world implementation of secondary findings management in Malaysia. The findings provide a baseline for understanding current clinical practice and may support future development of structured management pathways for patients and families receiving clinically actionable secondary findings.

5.6.2 Limitations of the Study

Despite these strengths, several limitations should be considered when interpreting the findings. First, the retrospective study design relied on the availability and completeness of existing clinical records. Some information, particularly regarding follow-up, clinical surveillance, and cascade testing, may not have been consistently documented. Therefore, the absence of documentation should not necessarily be interpreted as definitive evidence that a clinical action did not occur.

Second, the final sample size was relatively small, comprising 27 patients with secondary findings. This was partly attributable to the relatively low occurrence of secondary findings and the exclusion of six patients due to management at an external site, inaccessible clinical records, or non-attendance at the result disclosure appointment. The small sample size limits the extent of statistical analysis and the generalisability of the findings to other populations and healthcare settings.

Third, the study was conducted within genetic services and included patients who underwent WES for clinical indications. Therefore, the findings may not be representative of all individuals undergoing genomic testing in Malaysia, particularly those managed outside specialised genetic services.

Fourth, the assessment of clinical management was limited by the availability and duration of follow-up records. Some secondary findings require long-term surveillance and management, and the available observation period may not have captured subsequent clinical actions or long-term outcomes. Similarly, cascade testing outcomes were assessed based on documented information and may not reflect testing subsequently performed outside the participating centres.

Fifth, the study focused on documented clinical management and did not assess patient-reported outcomes. Factors such as patients' understanding of secondary findings, psychological responses, satisfaction with genetic counselling, and perceived barriers to follow-up or cascade testing were therefore not directly evaluated. Consequently, the underlying reasons for incomplete follow-up or limited cascade testing uptake could not be determined from this study.

Finally, the findings reflect the clinical practices and available services within the participating centres. Differences in referral practices, availability of specialised services, and follow-up procedures may influence the observed management outcomes. Therefore, the findings should be interpreted within the context of the participating genetic services and may not fully represent national practice.

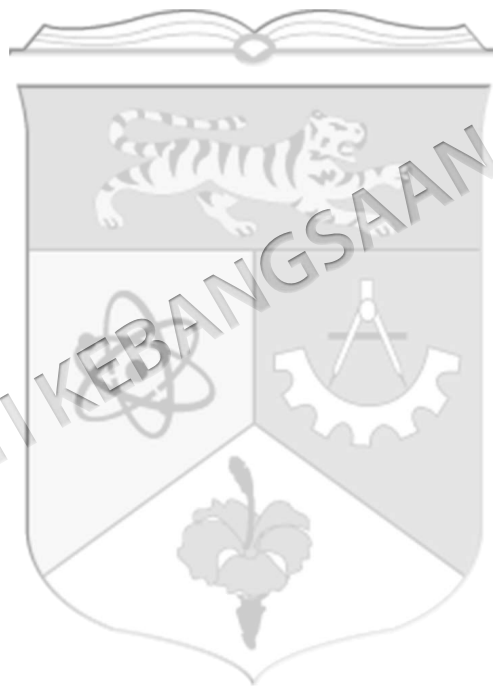
5.7 PROPOSED FRAMEWORK FOR MANAGEMENT OF SECONDARY FINDINGS

Figure 5.1 illustrates the proposed management framework for secondary findings identified through Whole Exome Sequencing (WES). The framework begins with WES, bioinformatics analysis, and identification and classification of secondary findings, followed by validation by the clinical genetics team, result disclosure, and patient and family counselling. Patients are then referred to relevant specialists for further management and clinical surveillance, while cascade testing is offered to first- and second-degree relatives.

The framework also considers factors that may affect the implementation of recommended management, including patient and family engagement, socioeconomic factors, healthcare accessibility, health literacy, follow-up adherence, and financial considerations. A financial and access assessment is included before cascade testing to identify potential barriers, particularly the cost and accessibility of genetic testing. Where barriers are identified, alternative support options may be explored, including government or public assistance, charitable or religious assistance, alternative testing strategies, and practical support in accessing testing services.

A family testing update and follow-up tracking system are also incorporated to document the status of cascade testing, including completed, declined or deferred, and pending testing. The system allows continued monitoring of patient follow-up, clinical outcomes, and changes in clinical or financial needs, allowing management plans to be updated when necessary.

Overall, the proposed framework provides a structured and patient-centred approach to the management of secondary findings by integrating clinical management, family testing, and follow-up. It may support more consistent management, improve access to appropriate genetic and clinical services, and promote continuity of care for patients and their families.



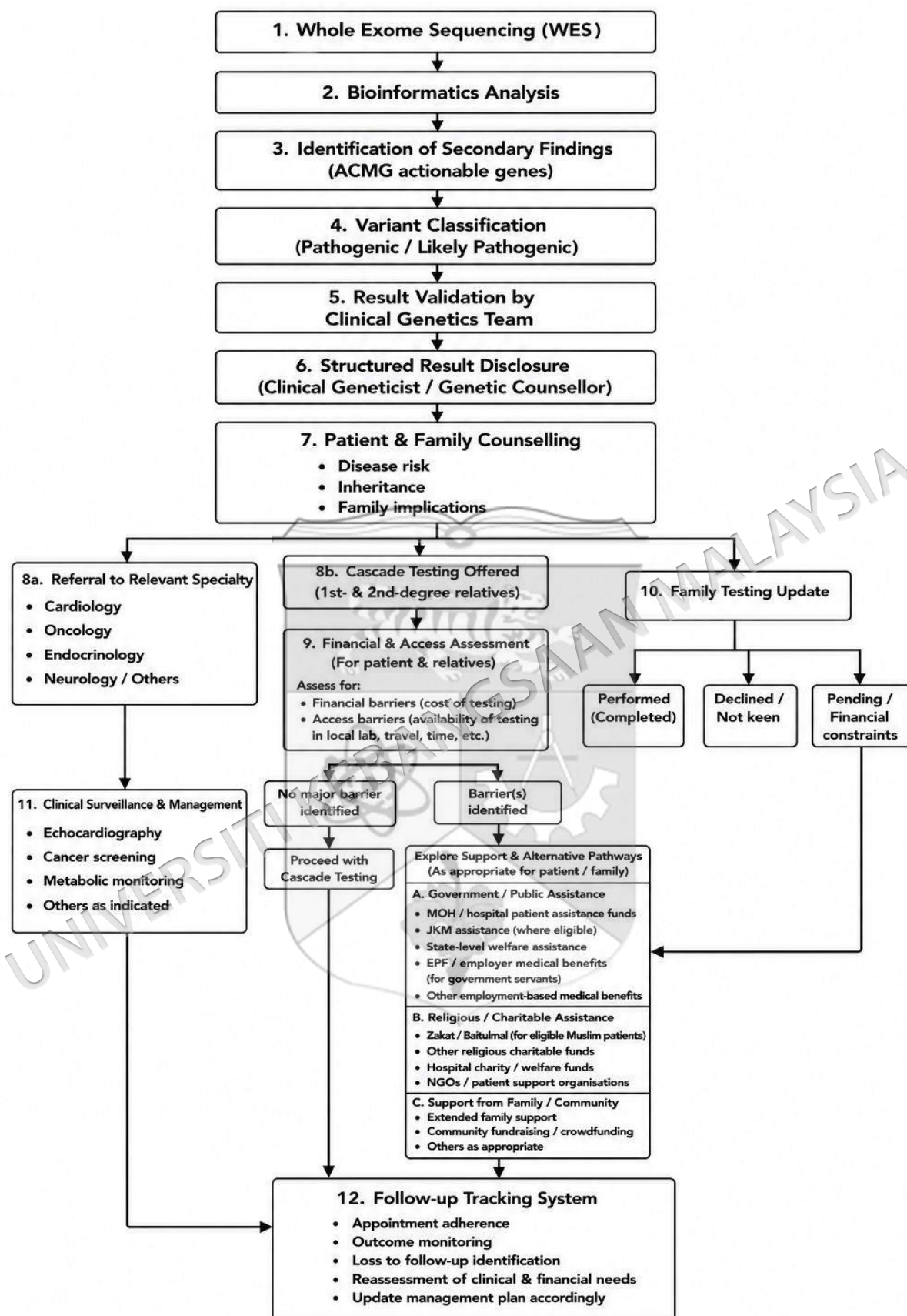


Figure 5.1 Proposed Framework for Management of Secondary Findings Identified through WES

5.8 RECOMMENDATIONS

5.8.1 Development of a Structured National or Institutional SF Pathway

A standardised institutional workflow should be developed for the management of secondary findings. This should include clear processes for result disclosure, referral pathways, and structured follow-up tracking to ensure uniformity in clinical practice.

5.8.2 Strengthening Follow-Up Monitoring Systems

A structured registry or tracking system is recommended to monitor:

1. Referral completion
2. Clinic attendance
3. Surveillance outcomes
4. Loss to follow-up cases

This would improve continuity of care and reduce missed clinical interventions.

5.8.3 Improving Cascade Testing Uptake

Strategies to enhance family-based genetic testing should include:

1. Financial support or increase slots for subsidized testing
2. Enhanced genetic counselling on familial risk
3. Telemedicine-based family outreach
4. Education materials for relatives

5.8.4 Enhancing Genetic Counselling Services

Genetic counselling services should be strengthened to ensure:

1. Consistent documentation of counselling sessions
2. Standardization of counselling practice
3. Expanding genetic counsellor workforce support
4. Improving counselling for complex or emotionally challenging results

5.8.5 Multidisciplinary Integration

Closer collaboration between genetics and clinical specialties (cardiology, oncology, endocrinology, neurology) should be enhanced to ensure timely surveillance and management of patients with actionable variants.

5.8.6 Policy and Institutional Development

Healthcare institutions should consider:

- Development of institutional guidelines for secondary findings management.
- Establishment of funding mechanisms for cascade testing.
- Integration of secondary findings pathways into national genomic medicine frameworks.

5.9 FINAL STATEMENT

Secondary findings from Whole Exome Sequencing (WES) represent an important opportunity for early disease detection and the implementation of preventive healthcare strategies. These findings extend the clinical value of genomic testing beyond the primary diagnostic indication, particularly for conditions where early surveillance and intervention can significantly improve patient outcomes.

However, the full clinical utility of secondary findings is highly dependent on several interconnected factors, including effective communication of results, patient understanding of clinical relevance, and the availability of structured follow-up pathways. In addition, consistent engagement between patients and healthcare providers, as well as timely referral to relevant clinical services, are essential to ensure that genomic information is translated into meaningful clinical action.

Challenges such as loss to follow-up, variability in patient readiness, socioeconomic constraints, and system-level limitations may reduce the effectiveness of post-test management. These issues highlight the importance of strengthening coordination within genomic services, including improved tracking systems and multidisciplinary collaboration, to support continuity of care.

Overall, enhancing these components is essential to maximise the impact of genomic medicine in routine clinical practice and to ensure that the benefits of secondary findings are fully realised in a sustainable and equitable manner.

CHAPTER VI

CONCLUSION

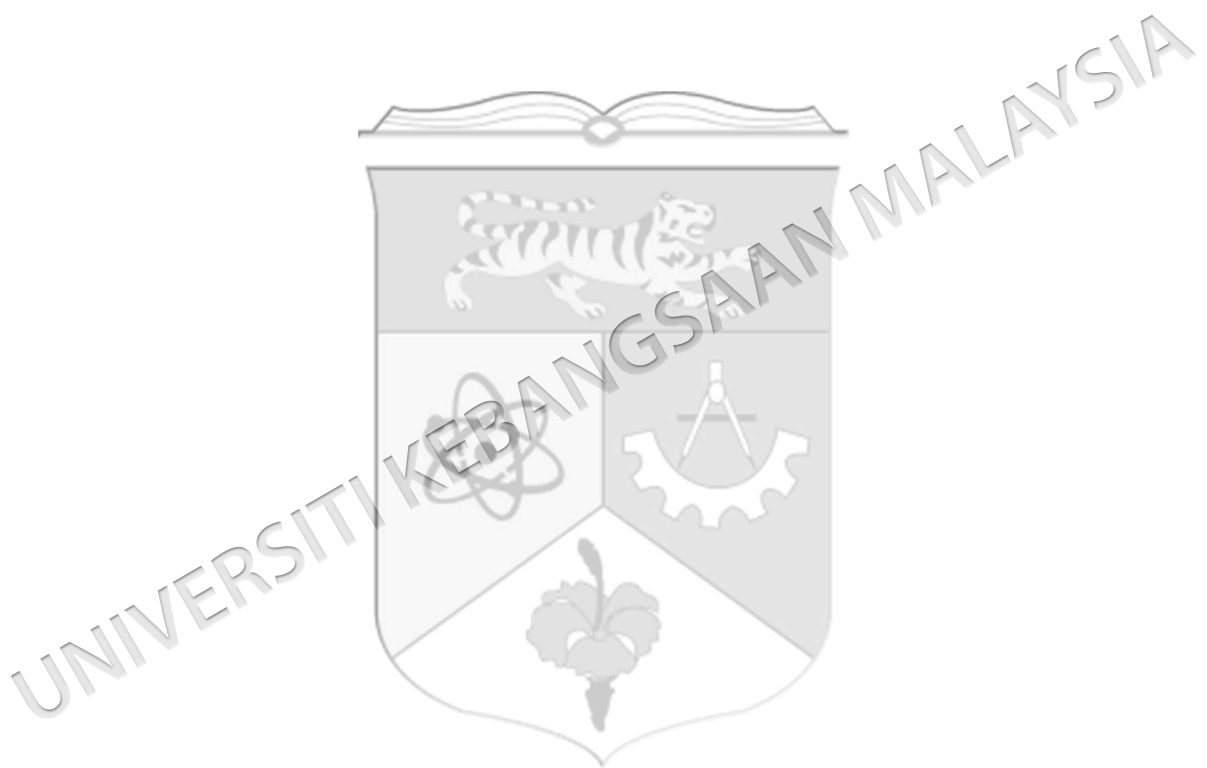
6.1 CONCLUSION

This study demonstrated that secondary findings identified through Whole Exome Sequencing (WES) were clinically relevant and required multidisciplinary management and continued follow-up. Among the 790 patients who consented to secondary findings disclosure, 33 patients were identified with secondary findings. Following the exclusion of six patients based on the predefined exclusion criteria, 27 patients were included in the final analysis, with a total of 28 secondary findings identified across 17 genes.

The clinical management of these findings involved genetic counselling, referral to relevant medical specialties, clinical surveillance, and the offer of cascade testing to at-risk relatives. Although genetic counselling and referral were generally implemented, completion of recommended clinical follow-up and cascade testing was variable. These findings indicate that the identification of a secondary finding does not necessarily translate into completion of the recommended clinical management pathway.

Overall, this study highlights that the clinical utility of WES extends beyond the primary indication for testing, but the effectiveness of secondary findings disclosure depends on subsequent clinical implementation and family engagement. The findings support the need for structured management pathways to facilitate consistent follow-up, surveillance, and cascade testing following the identification of secondary findings. Such pathways may help strengthen the integration of secondary

findings into routine genomic medicine and improve the clinical benefit derived from WES.



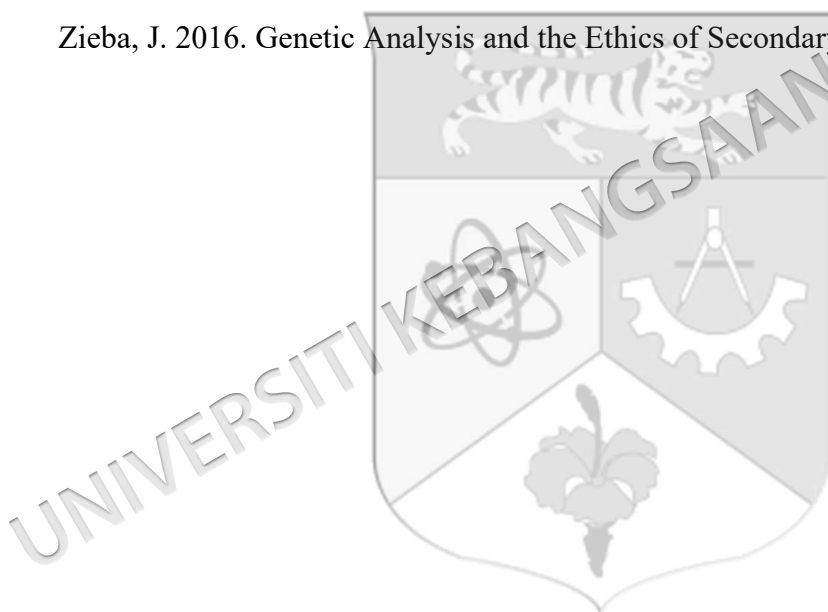
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APPENDIX A

DATA COLLECTION SHEET

DATA COLLECTION CHECKLIST

Data Collection Checklist: Secondary Findings in WES (ACMG 3.3 SECONDARY FINDINGS GENE LIST)

SECTION A: Patient Demographics

Item	Details	✓
Patient ID		☐
Date of birth		☐
Age at time of test		☐
Sex	Male / Female	☐
Ethnicity	Malay / Chinese / Indian Others:	☐

SECTION B: Testing Information

Item	Details	✓
Diagnosis		☐
Type of genetic test performed	WES	☐
Report date		☐
Family History (Any family history relevant to the Secondary Finding? Include condition, relative, and age if known.)		☐

SECTION C: Secondary Findings (SF)

Item	Details	✓
Secondary finding detected?	Yes	☐
Gene involved	BRCA1 / LDLR / Other: _____	☐
Variant classification	Pathogenic / Likely Pathogenic	☐
Disease association		☐
Secondary Finding report shared to patient? (Includes giving a copy of the report and verbal explanation)	Yes / No	☐

SECTION D: Management of SF			
Item	Details	✓	Explanation
Referral made after genetic clinic visit If no (why)	Yes / No	☐	Reason if No:
Type of referral	Oncology / Cardiology / Other: _____	☐	
Cascade testing offered to 1st- and 2nd-degree relatives? If No (Why)	Yes / No	☐	To who? 1 st degree: 2 nd degree: Reason if No:
Family members tested If no (why)	Yes / No / No data	☐	Reason if No:
Preventive/surveillance action taken by patient	Yes / No / No Data	☐	Outcome:
Type of action (specify, detail)	Screening / Surgery / Lifestyle / Other: / No data	☐	Outcome:
Genetic counseling provided?	Yes	☐	
By whom	Genetic Counselor / Clinical Geneticist / Other :	☐	
Topics discussed	Disease Risk, inheritance, family implication, etc.	☐ Disease Risk ☐ Inheritance ☐ Family implication	Outcome:
SECTION E: Outcomes			
Item	Details	Explanation	✓
Patient follow-up on genetic clinic referral?	Yes / No / Unknown		☐
Compliance with medical advice (Did the patient follow the doctor's recommendations?)	Yes / No		☐
Reason for non-compliance (if any)			☐

Checklist adapted based on key principles from ACMG Secondary Findings 3.3 Guidelines and clinical follow-up practices.

APPENDIX B

JPEUKM APPROVAL LETTER



FAKULTI PERUBATAN • FACULTY OF MEDICINE

Reference: UKM.FPR.SPI 800-2/27

Date : 28 November 2025

Associate Professor Dr Adli Ali
Department of Paediatrics
Faculty of Medicine, UKM

Dear Dr,

APPROVAL TO CONDUCT RESEARCH IN HOSPITAL TUNKU AMPUAN BESAR TUANKU AISHAH ROHANI, HOSPITAL PAKAR KANAK-KANAK UKM

Title : Secondary Findings in Whole Exome Sequencing: Prevalence and Management

Project Code : FF-2025-501

With reference to the above, the Faculty of Medicine UKM and Hospital Tunku Ampuan Besar Tuanku Aishah Rohani, Hospital Pakar Kanak-Kanak UKM (Hospital TABTAR) has approved the above study based on the following information:

Duration of Research	13 November 2025 – 12 November 2026
Financial Support	Without Financial Assistance

A Progress Report should be submitted through SMPU system every six (6) months from the date of approval and a Final Report within three (3) months after expiration of the study approval. Failure to submit the Final Report will affect the application of research and financial support in the future.

Please register the research at the National Medical Research Register (www.nmrr.gov.my) if involved any use of infrastructure/organization/facility/staff/students/patients in the hospital/clinic/organization under the Ministry of Health Malaysia. Researchers must also ensure that notification to the Ministry of Health is made if any results of this research project are to be published in a journal or presented at a conference.

For your information, a copy of the approval letter for co-researchers and students will be send via e-mail. Please to be reminded of these project can only be carried out after obtaining a certificate and letter of approval by UKM Ethics Committee.

Thank you.



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APPENDIX C

NMRR APPROVAL LETTER



JAWATANKUASA ETIKA & PENYELIDIKAN PERUBATAN
(Medical Research & Ethics Committee)
 KEMENTERIAN KESIHATAN MALAYSIA
 d/a Kompleks Institut Kesihatan Negara
 Blok A, No 1, Jalan Setia Murni U13/52,
 Seksyen U13, Bandar Setia Alam,
 40170 Shah Alam, Selangor.



Tel: 03-3362 8888/8205

Ref : 26-00287-NCW (2)
 Date: 31-March-2026

ASSOCIATE PROFESSOR DR. ADLI BIN ALI
HOSPITAL TUNKU AMPUAN BESAR TUANKU AISHAH ROHANI
HOSPITAL PAKAR KANAK-KANAK UKM

Dear Sir/ Mdm,

ETHICS INITIAL APPROVAL: NMRR ID-26-00287-NCW (IIR)
Secondary Findings in Whole Exome Sequencing: Prevalence and Management

This letter is made in reference to the above matter.

2. The Medical Research and Ethics Committee (MREC), Ministry of Health Malaysia (MOH) has provided ethical approval for this study. Please take note that all records and data are to be kept strictly **CONFIDENTIAL** and can only be used for the purpose of this study. All precautions are to be taken to maintain data confidentiality. **Permission from the District Health Officer / Hospital Administrator / Hospital Director and all relevant heads of departments / units where the study will be carried out must be obtained prior to the study.** You are required to follow and comply with their decision and all other relevant regulations.

3. The investigators and study sites involved in this study are:

HOSPITAL PAKAR KANAK-KANAK UKM
 Adli Bin Ali (Principal / Coordinating Investigator)
 Sharifah Azween Binti Syed Omar
 Nur Mashitah Binti Mohd Shahrom
 Jasmine Lee

HOSPITAL KUALA LUMPUR
 Muzhirah Aisha Binti Md Haniffa
 Keng Wee Teik

4. The following study documents have been received and reviewed with reference to the above study:

Documents received and reviewed with reference to the above study:

1. Study Protocol Version 4.0, dated 12-Mar-2026
2. Cover Letter to MREC Version 2.0, dated 11-Dec-2025
3. Declaration of Conflict of Interest (COI form) Version 2.0, dated 05-Feb-2026
4. Clinical Form Report / Data Collection Form Version 2.0, dated 12-Mar-2026
5. Investigator's documents : Declaration of Conflict of Interest (COI), IA-HOD-IA, and CV:
 - a) Adli Bin Ali (Principal / Coordinating Investigator)
 - b) Sharifah Azween Binti Syed Omar
 - c) Nur Mashitah Binti Mohd Shahrom
 - d) Jasmine Lee
 - e) Muzhirah Aisha Binti Md Haniffa
 - f) Keng Wee Teik