MINISTRY OF HEALTH
SINGAPORE

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09 June 2025

Please refer to distribution list

INTRODUCTION OF FAMILIAL HYPERCHOLESTEROLAEMIA (FH) GENETIC TESTING SERVICE

This circular informs healthcare institutions and registered medical practitioners on the introduction of Familial Hypercholesterolaemia (FH) Genetic Testing as a mainstream clinical service from 30 June 2025.

FAMILIAL HYPERCHOLESTEROLAEMIA

2. FH is an inherited genetic condition that predisposes FH patients to early onset atherosclerotic cardiovascular disease (ASCVD) due to impaired low-density lipoprotein cholesterol (LDL-C) metabolism. FH affects an estimated 20,000 Singapore residents and carries a high risk of major adverse cardiovascular events, leading to significant morbidity and mortality. Early detection through index genetic testing and cascade screening, and intervention through the administration of intensive lipid-lowering therapies can substantially reduce the risk of cardiovascular complications and improve outcomes.

SERVICE OVERVIEW

3. In line with the Ministry of Health (MOH)'s efforts to enhance preventive care, a new FH Genetic Testing service will be introduced to support early identification of patients with FH. This will involve the following:

a) Establishment of the Genomic Assessment Centre (GAC);
b) Identification of high-risk index patients and referral to the GAC by physicians (based on the GAC FH referral criteria);
c) Genetic testing of these referred patients (**"FH index genetic testing"**) at the GAC; and
d) Subsequent screening for first-degree relatives of patients who test positive for FH ("**cascade screening**").

4. On initial roll-out, only Singapore Citizens / Permanent Residents (SCs/PRs) will be eligible for genetic testing at the GAC. This applies to both FH index genetic testing and cascade screening.

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ESTABLISHMENT OF THE GAC

5. The GAC is the specialised facility for genetic testing services within each cluster. The GAC will serve as a dedicated clinic where patients can undergo genetic testing and receive genetic counselling to understand the benefits and implications of genetic testing and facilitate cascade screening of family members. Physicians may start referring patients who meet the referral criteria for FH index genetic testing to the first GAC operated by Singapore Health Services (SingHealth) from **30 June 2025**. This GAC will serve all Singapore residents until additional centres open. GACs operated by National Healthcare Group (NHG) and National University Health System (NUHS) will be established within the next year.

GAC REFERRAL CRITERIA FOR FH INDEX GENETIC TESTING

6. For FH index genetic testing at the GAC, SCs/PRs may be referred only if they meet the criteria of **LDL-C ≥ 5.5 mmol/L (≥ 212 mg/dL)** ("**GAC FH referral criteria**"). Please refer to **Annex A-1** for a flowchart of the consolidated referral criteria and subsidy criteria for **FH index genetic testing** in the GAC.

7. In order for the GAC to verify the referred patient's eligibility based on LDL-C cut-off, referring physicians should:

a) Indicate the referred patient's LDL-C level and date of the LDL-C test in the referral letter to the GAC; and
b) Ensure that the medical/laboratory report documenting the referred patient's LDL-C level is available on the National Electronic Health Records (NEHR) or attach a copy of the report with the referral letter to the GAC. Physicians may also advise their patients to bring a copy of their medical/laboratory report to their GAC appointment for verification.

8. For more details regarding referral workflows from various referral sources to the GAC, please refer to **Annex B** and the guide for genetic testing and management of FH in primary care, which will be circulated to all primary care physicians (PCPs) separately.

CLINICAL WORKFLOW

9. Upon verification of the referred patient's eligibility for FH index genetic testing, the GAC will conduct the following (refer to **Annex C** for a diagram of the clinical workflow):

a) Pre-genetic test counselling, financial counselling, consent-taking;
b) FH index genetic testing via an FH gene panel comprising of the *LDLR*, *APOB, and PCSK9* genes only;
c) Post-genetic test counselling and uploading of a GAC report to NEHR, with a copy of the report provided to the patient;[1] and

[1] Genetic test results will be accessible via the patient's NEHR and HealthHub. A separate GAC report will also be accessible via the patient's NEHR under the referral notes section, with a copy provided to the patient.

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d) Cascade screening for eligible and consenting SC/PR first-degree relatives (i.e., parents, siblings, and children) if the referred patient tests positive for a pathogenic variant in any one of the three FH-associated genes analysed during FH index genetic testing.

DIAGNOSIS AND MANAGEMENT OF SUSPECTED AND CONFIRMED FH

10. The diagnosis of FH in a patient who tests positive for a pathogenic variant in an FH-associated gene will be made in conjunction with the presence of a suggestive clinical history, physical examination and/or abnormal non-genetic laboratory tests (i.e., raised LDL-C levels). The diagnosis of FH may be aided by the Dutch Lipid Clinic Network Score (DLCNS) for FH.

11. The clinical management of hypercholesterolaemia, regardless of the status or results of the genetic testing, shall remain the responsibility of the referring physician. Physicians are recommended to manage patients with hypercholesterolaemia in accordance with prevailing national guidelines.[2] This includes, but is not limited to:

a) Non-pharmacological management of hypercholesterolaemia;
b) Pharmacological management of hypercholesterolaemia;
c) Assessment for the clinical diagnosis of FH;
d) Ruling out of secondary causes of hypercholesterolaemia where relevant;
e) Clinical and biochemical monitoring of lipid control;
f) Tracing of genetic test results and adjustment of patient's treatment and LDL-C targets; and
g) Referral to relevant specialists for special patient populations if required (e.g., paediatric endocrinology for paediatric patients).

12. As much as possible, referring physicians should **encourage eligible patients and first-degree relatives to receive FH index genetic testing and cascade screening respectively**, so that proactive measures can be taken to reduce ASCVD risk.

13. In the event where a patient tests positive for a pathogenic variant in an FH-associated gene but is not on active follow-up (e.g., if the patient was identified through cascade screening), the GAC will advise the patient to visit a PCP for follow-up.

[2] Agency for Care Effectiveness (ACE). Lipid management: focus on cardiovascular risk. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. Available from: go.gov.sg/acg-lipid-management

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SUBSIDIES AND MEDISAVE USE FOR FH GENETIC TESTING

Subsidy at the GAC

14. To qualify for subsidised FH genetic testing, **index patients** must meet the GAC FH referral criteria (para 6) and be referred from one of the following eligible referral sources:

i. CHAS GP clinics, for CHAS/PG/MG cardholders only; or
ii. Polyclinics; or
iii. Subsidised SOC in PHIs

15. First-degree SC/PR relatives of an index patient who tested positive for FH at the GAC can receive subsidies for cascade screening. For avoidance of doubt, first-degree relatives of an unsubsidised index patient are eligible to receive subsidy for the cascade screening. Means-tested subsidies of up to 70% under the SOC subsidy framework will be provided to eligible patients.

16. SCs / PRs who meet the GAC FH referral criteria but not the subsidy criteria may still undergo unsubsidised FH genetic testing at the GAC.

MediSave use at the GAC

17. Both subsidised and unsubsidised patients who meet the GAC FH referral criteria can tap on MediSave under the MediSave500/700 scheme, as part of the Chronic Disease Management Programme (CDMP). The amount of MediSave utilised is subject to the prevailing 15% copayment for CDMP. Patients and first-degree relatives who are 60 years old and above may also utilise Flexi-MediSave to offset any remaining cost. Typically, only patients diagnosed with one or more CDMP conditions may tap on the MediSave 500/700 limits for treatments under the CDMP. Nevertheless, MOH will allow an exception for first-degree relatives, who are identified for FH cascade screenings, to also tap on the MediSave 500/700 limits even if they are not diagnosed with a CDMP condition. This arrangement seeks to facilitate quicker access to MediSave for patients requiring such screenings, and will stand until further notice.

Summary of Subsidy and MediSave eligibility at GAC

18. For reference, **Annex A-1** provides a diagrammatic overview of the citizenship criteria, GAC FH referral criteria, and subsidy criteria for index patients. **Annex A-2** provides a diagrammatic overview of the cascade testing criteria at the GAC.

Subsidy and MediSave eligibility for follow-up care

19. Follow-up at primary care. Patients who test positive for FH and seek follow-up at primary care may be eligible for subsidies and to tap on MediSave (under the MediSave 500/700 limits), depending on the criteria in the specific setting where care is sought, per **Table 1**.

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Table 1. Subsidy and MediSave eligibility at different primary care settings

Care setting	Subsidy eligibility	MediSave eligibility
Polyclinics	SCs and PRs receive up to 75% subsidy for drugs and services	SCs and PRs can claim under MediSave500/700 subject to 15% co-payment requirement. Flexi-MediSave may also be used to cover any remaining copayment, including the 15% co-payment for claims for CDMP treatment. 15% cash co-payment waived for HSG enrolees at their enrolled clinic
Healthier SG (HSG) GP to whom patient is enrolled	Enrolees who are PG/MG/CHAS cardholders receive: • Percentage-based HSG Chronic Tier subsidies* for drugs on the HSG Medication List • Dollar-based subsidies for other care components *Percentage-based subsidies for some drugs on the HSG Medication List are available only for CHAS Blue/Orange cardholders, or PG/MG cardholders who also hold a CHAS Blue/Orange card.	
Other CHAS GPs	PG/MG/CHAS cardholders receive dollar-based CHAS subsidies	SCs and PRs can claim under MediSave500/700 subject to 15% co-payment requirement. Flexi-MediSave may also be used to cover any remaining copayment, including the 15% co-payment for claims for CDMP treatment.

20. Follow-up at SOCs.

a) **Index patients** who are referred to an SOC for follow-up will be subsidised for their follow-up treatment, if the referral meets the subsidised referral criteria.

b) For **cascade patients**, whose care episode did not originate from a PCP, they will be advised to follow-up with a PCP. If they are subsequently referred by the PCP to follow up at an SOC, they can be subsidised for the follow-up treatment if the referral meets the subsidised referral criteria.

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MEDISAVE CLAIM SUBMISSION

21. National Platform for Healthcare Claims (NPHC) has been enhanced from 1 June 2025 to allow for MediSave claims[3] for FH index genetic testing and cascade screening. For such claims, please use the following charge code – diagnosis code pairings in **Annex D**. MediSave claims should only be done at GACs after they have commenced operations.

PRICES FOR FH TESTING

22. The indicative price range for the (i) visit at the GAC and (ii) potential follow-up treatment are summarised in **Annex E**. Primary care providers and the GAC should convey the indicative price range to patients during consultations or financial counselling where relevant.

FOR CLARIFICATIONS

23. For any clarifications on this circular, please email moh_info@moh.gov.sg.

PROFESSOR KENNETH MAK
DIRECTOR-GENERAL OF HEALTH
MINISTRY OF HEALTH

[3] MOH Healthcare Claims Portal (MHCP) will also be enhanced to allow GPs to submit MSV claims for cascade screening cases through additional selection of diagnosis code.

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All General Practitioners Clinics (CHAS and non-CHAS)

Primary Care Networks

All Registered Doctors

Annexes

Annex A-1	Consolidated Referral & Subsidy Criteria for FH Index Genetic Testing in the GAC
Annex A-2	Consolidated Clinical & Subsidy Criteria for Cascade Screening in the GAC
Annex B	Referral Source & Workflow
Annex C	Clinical Workflow for FH Index Genetic Testing in the GAC
Annex D	Charge Code and Diagnosis Pairings (for MSV)
Annex E	Indicative Price Ranges for FH Testing and Follow-Up Care
Annex F	Frequently Asked Questions (FAQs)

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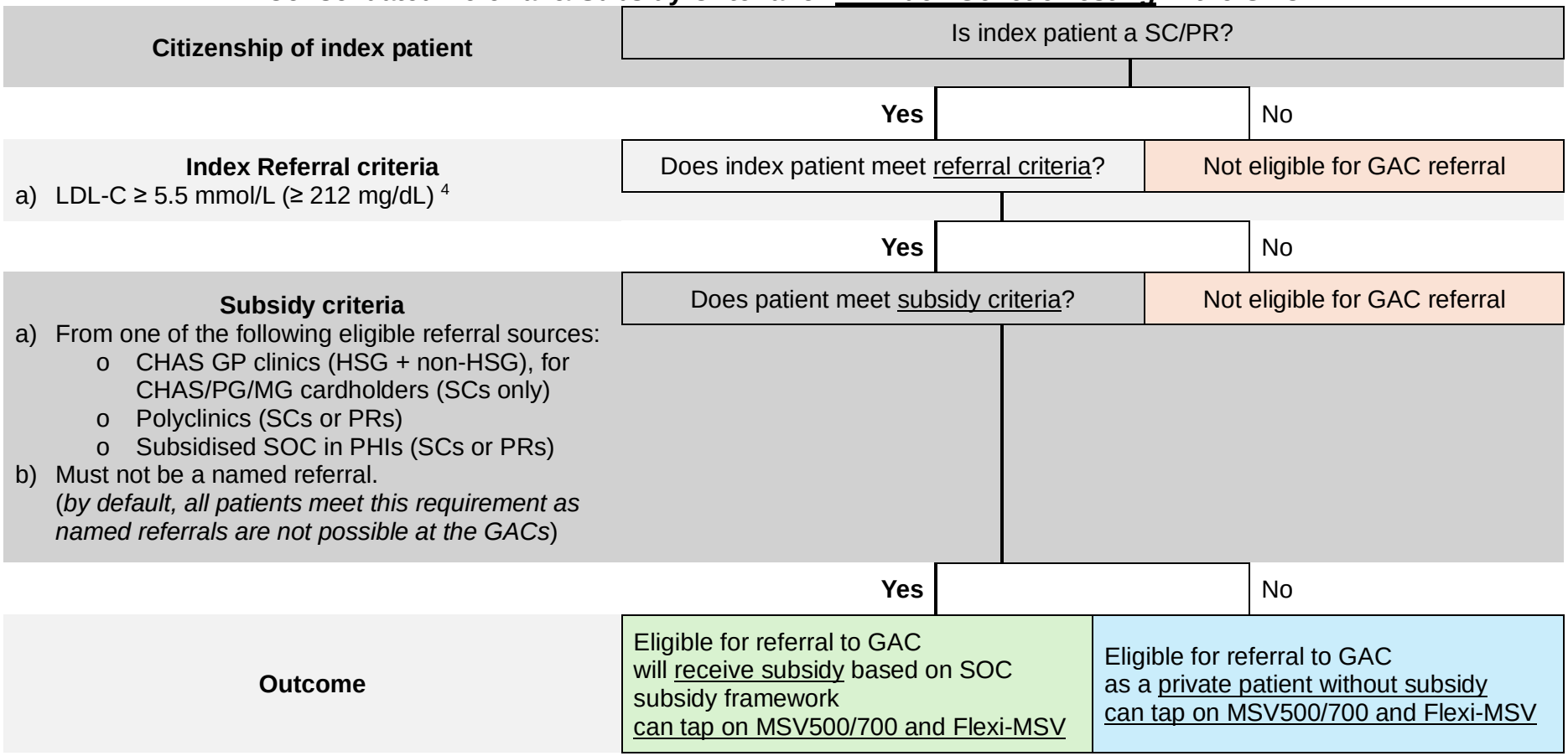
Annex A-1

Consolidated Referral & Subsidy Criteria for FH Index Genetic Testing in the GAC



Abbreviations: CHAS, Community Health Assist Scheme; GAC, Genomic Assessment Centre; GP, General Practitioner; HSG, Healthier-SG; LDL-C, low-density lipoprotein cholesterol; MG, Merdeka Generation; PG, Pioneer Generation; PHI, Public Healthcare Institutions; SOC, Specialist Outpatient Care (Clinic); SC/PR, Singapore Citizen / Permanent Resident.

[4] Historical or overseas LDL-C test results indicating levels ≥ 5.5 mmol/L are allowed but must be well-documented, and these reports should be included in the referrals to the GAC.

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Annex A-2

Consolidated Clinical & Subsidy Criteria for Cascade Screening in the GAC

Citizenship of Cascade Patient	Is cascade patient a SC/PR?	
	Yes	No
Cascade Clinical Criteria a) Cascade is a first-degree relative of an index patient who tested positive for FH at the GAC.	Does cascade patient meet clinical criteria?	Not eligible for GAC cascade screening
	Yes	No
Outcome [5]	Eligible for cascade screening in GAC will receive subsidy based on SOC subsidy framework can tap on MSV500/700 and Flexi-MSV	Not eligible for GAC cascade screening

Abbreviations: GAC, Genomic Assessment Centre; SOC, Specialist Outpatient Care (Clinic); SC/PR, Singapore Citizen / Permanent Resident

[5] The subsidy status of the cascade patient is independent of the index patient (i.e., first-degree relative). For an index patient who undergoes index genetic testing at a private (non-subsidised rate), the private index patient's first-degree relatives can still receive subsidised cascade screening at the GAC.

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Annex B

Referral Source & Workflow

Referral Source	Subsidised at GAC (for index patients)?	Referral Workflow
Primary Care		
CHAS GPs		HSG GPs Via Clinic Management System (preferred) *or* Non-HSG GPs Via CHAS Referral Form
- *CHAS, PG, MG cardholders*	Yes	
- *Non-CHAS/PG/MG cardholders*	No	
Non-CHAS GPs	No	E-mail to KKH central appointment at centralappt@kkh.com.sg
SingHealth Polyclinics	Yes	E-mail to KKH central appointment at referral@kkh.com.sg
Non-SingHealth Polyclinics	Yes	E-mail to KKH central appointment at centralappt@kkh.com.sg
SOCs		
SingHealth SOCs		E-mail to KKH central appointment at referral@kkh.com.sg
- *Subsidised clinic*	Yes	
- *Private clinic*	No	
Non-SingHealth PHIs' SOCs		E-mail to KKH central appointment at referral@kkh.com.sg
- *Subsidised clinic*	Yes	
- *Private clinic*	No	
Private Hospitals/Clinics	No	E-mail to KKH central appointment at centralappt@kkh.com.sg

Abbreviations: CHAS, Community Health Assist Scheme; GP, General Practitioner; MG, Merdeka Generation; PG, Pioneer Generation; PHI, Public Healthcare Institutions; SOC, Specialist Outpatient Care (Clinic).

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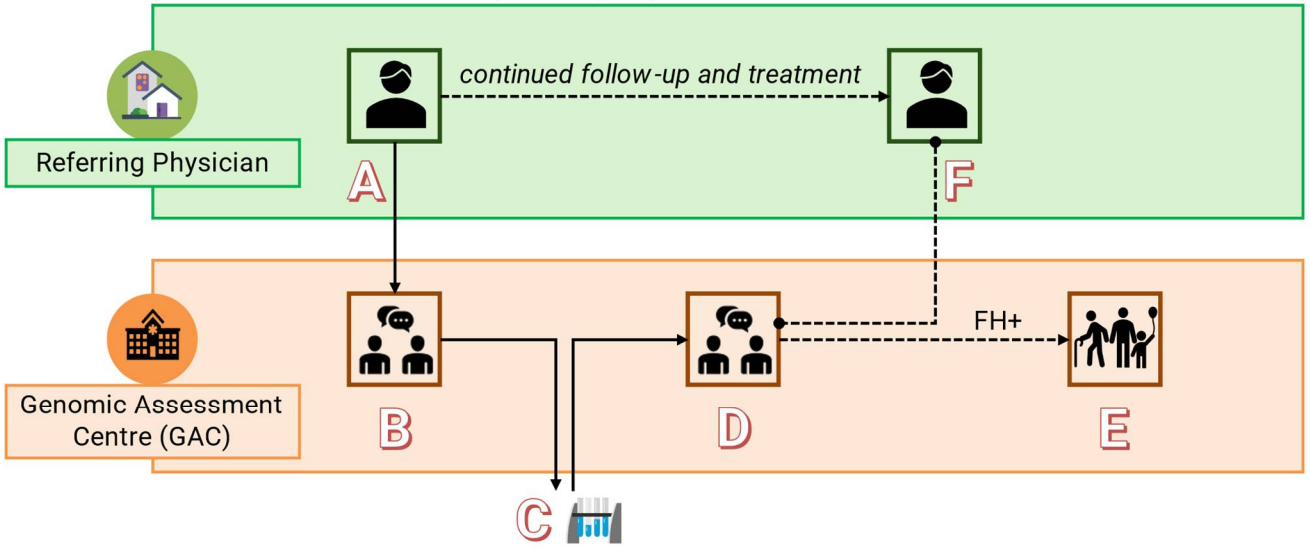
Annex C

Clinical Workflow for FH Genetic Testing in the GAC

A. Referral to GAC for eligible high -risk patients
Based on GAC referral criteria:
- SC/PR and
- LDL-C ≥ 5.5 mmol/L (≥ 212 mg/dL)

F. Referring Physicians trace GAC report
- Accessible via NEHR, with copy provided to patient
- ± Adjust treatment / LDL-C target



B. Pre-Genetic Test Care
- Genetic counselling
- Financial counselling
- Consent-taking for genetic testing
- Consent-taking to contact first-degree relatives for cascade screening if FH+
- Phlebotomy

C. Genetic Test in Lab

D. Post-Genetic Test Care
- Counselling on test results & interpretation
- Uploading of GAC report to NEHR, with copy provided to patient

E. Cascade Screening for SC/PR first-degree relatives of FH+ cases
- Repeat B to D

Abbreviations: LDL-C, low-density lipoprotein cholesterol; SC/PR, Singaporean Citizen or Permanent Resident; NEHR, National Electronic Health Records

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Annex D

Charge code – Diagnosis pairings for FH testing and screening

<table>
<tr><th></th><th>Charge code</th><th>Diagnosis code</th></tr>
<tr><td><u>FH index genetic testing</u></td><td>CV0003 if patient has Lipid Disorder (hyperlipidaemia) only

Or

CC0003 if patient has Lipid Disorder (hyperlipidaemia) (e.g. Familial Hypercholesterolaemia) complicated by Peripheral Vascular Disease (I739)</td><td>E780 – E785, I739 (based on patient's medical history)

<table>
<tr><td>E780</td><td>Pure hypercholesterolaemia</td></tr>
<tr><td>E781</td><td>Pure hyperglyceridaemia</td></tr>
<tr><td>E782</td><td>Mixed hyperlipidaemia</td></tr>
<tr><td>E783</td><td>Hyperchylomicronaemia</td></tr>
<tr><td>E784</td><td>Other hyperlipidaemia</td></tr>
<tr><td>E785</td><td>Hyperlipidaemia, unspecified</td></tr>
<tr><td>I739</td><td>Peripheral vascular disease, unspecified</td></tr>
</table></td></tr>
<tr><td><u>FH cascade screening</u> for first degree relatives</td><td>CV0003</td><td>Z01

<table>
<tr><td>Z01</td><td>Other special examinations and investigations of persons without complaint or reported diagnosis</td></tr>
</table></td></tr>
</table>

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Annex E

Indicative price ranges for FH testing and follow-up care

	Pre-subsidy price			**After subsidies**	**After subsidies and MSV500^**
GAC visit*	**Proband**		$764	$117 - $575	$18 - $87
	Cascade		$334	$53 - $253	$8 - $38
	Pre-subsidy price (annual basis)			**After subsidies**	**After subsidies and MSV500^**
Follow-up treatment at primary care	**Polyclinics^^**	Only statins and/or Ezetimibe	$146 - $292	$19 - $220	$0
		Statins, Ezetimibe and Evolocumab	$3298	$414 - $3226	$0 - $2726
	HSG GP where patient is enrolled^^	Only statins and/or Ezetimibe	$146 - $292	$19 - $146	$0
		Statins, Ezetimibe and Evolocumab	$3298	$414 - $3152	$0 - $2652
	For Non-HSG CHAS GP or HSG GP where patient is not enrolled, pre-subsidy prices are as determined by clinics. CHAS dollar-based subsidies will apply to CHAS cardholders				

**Comprises pre-screening counselling, phlebotomy, FH screening test, and post-screening counselling*

^Assumes patient does not have a complex chronic CDMP condition, and has full MSV500 balance left; otherwise, the annual limit will be $700 instead. Seniors of 60 years old and above may also utilise Flexi-MediSave to pay for the remaining cost in addition to MSV500/700.

^^Assumes patient is enrolled under HSG at polyclinic or HSG GP for wavier of 15% co-payment for CDMP

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Annex F

Frequently Asked Questions (FAQs)

I. Referral criteria for FH genetic testing at GACs

1. Why is the LDL-C cut-off for GAC FH referrals set at ≥ 5.5 mmol/L (≥ 212 mg/dL)?

- This LDL-C cut-off in the GAC FH referral criteria takes into account epidemiological data from existing national screening programmes and the Precision Health Research Singapore (PRECISE) Clinical Implementation Pilot (CIP) on FH, vis-à-vis the projected capacity of the designated GAC at initial roll-out.
- Medical practitioners should note that the LDL-C cut-off in the GAC FH referral criteria differs from the LDL-C cut-off to clinically suspect FH. As stated in current Agency for Care Effectiveness (ACE) Clinical Guidance for Lipid Management,[6] FH should be suspected when LDL-C levels are > 4.9 mmol/L (> 190 mg/dL) in adults after excluding secondary causes.
- Following implementation, MOH will continue to review the GAC FH referral criteria and genetic testing protocols and will update clinical workflows as appropriate.
- For patients with LDL-C > 4.9 mmol/L (> 190 mg/dL) to < 5.5 mmol/L (< 212 mg/dL) who may benefit from genetic testing but do not meet the GAC referral criteria, refer to question 2 below.

2. Can patients with LDL-C > 4.9 mmol/L to < 5.5 mmol/L (> 190 mg/dL to < 212 mg/dL) be referred to GAC for subsidised FH genetic testing if there is clinical suspicion for FH?

- Genetic tests for FH done outside of the GAC will not be eligible for the subsidies stated in this circular.
- Physicians should not refer patients who do not meet the referral criteria of LDL-C ≥ 5.5 mmol/L (≥ 212 mg/dL) to the GAC.
- Physicians may consider referring patients who do not meet the referral criteria but may benefit from FH genetic testing to a relevant specialist outside of the GAC (as per the usual process for SOC referrals) for further evaluation.

3. Can patients with historical LDL-C results of ≥ 5.5 mmol/L (≥ 212 mg/dL) be referred to the GAC?

- Patients with historical LDL-C results of ≥ 5.5 mmol/L (≥ 212 mg/dL) (e.g., dated several years ago) can be referred to the GAC if these historical LDL-C results are clearly documented on an unambiguous and objective medical/laboratory report.
- In principle, these patients should be investigated for FH even if their current LDL-C results are < 5.5 mmol/L (< 212mg/dL) (regardless of whether they are currently on lipid-lowering therapy or not).

[6] Agency for Care Effectiveness (ACE). Lipid management: focus on cardiovascular risk. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. Available from: go.gov.sg/acg-lipid-management

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4. Can patients with overseas LDL-C results of ≥ 5.5 mmol/L (≥ 212 mg/dL) be referred to the GAC?

- The GAC can accept LDL-C tests done overseas if the referral criteria of ≥ 5.5 mmol/L (≥ 212 mg/dL) is met.
- The overseas LDL-C results should be clearly documented on an unambiguous and objective medical/laboratory report.

5. Can first-degree relatives (of patients who test positive for a pathogenic variant for FH) be referred directly to the GAC for cascade screening?

- For patients who receive FH index genetic testing in the GAC, if a pathogenic variant in any one of the three FH-associated genes (i.e., any of LDLR, APOB or PCSK9), the GAC will contact first-degree relatives of the patient (subject to the patient's consent) for cascade screening.
- In the event that a patient receives FH index genetic testing outside of the GAC and tests positive for a pathogenic variant for FH, first-degree relatives cannot be referred directly to the GAC for cascade screening. To note, first-degree relatives who have LDL-C levels that meet the referral criteria of LDL-C ≥ 5.5 mmol/L (≥ 212 mg/dL) can be referred to the GAC for FH index genetic testing.
- Following implementation, MOH will continue to review referral criteria and workflows to the GAC and will update clinical workflows as appropriate.

II. Referral source, subsidy criteria and MediSave use

6. Will all patients who are referred to GAC receive subsidies for FH genetic testing?

- No. Patients must meet all of the subsidy criteria stated in this circular to be eligible for subsidies.
- Patients who meet the GAC FH referral criteria (≥ 5.5 mmol/L (≥ 212 mg/dL)), but do not meet all of the subsidy criteria, may still be referred to GAC for non-subsidised FH genetic testing (e.g., referrals from non-CHAS GP / private SOC in PHI / private hospitals).
- Patients and first-degree relatives who meet the referral criteria, will be eligible to claim MediSave regardless of their subsidy status.

7. Will named referrals to the GAC be allowed?

- The GAC will primarily be staffed by Genetic Counsellors (GC), Genetic Counselling Associates (GCA), and executives. As such, named referrals are not applicable to GAC referrals since patients will not be under the care of any specific specialist.

III. Genetic testing

8. For index genetic testing, will other FH-associated genes (other than *LDLR*, *APOB*, *PCSK9*) be reported?

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- No, only the above stated genes will be analysed and reported in both the lab report and the GAC report.
- There are well-studied FH-causing pathogenic mutations for *LDLR*, *APOB*, *PCSK9* genes. In addition, these three genes have high penetrance and an autosomal dominant inheritance pattern with clear benefits for cascade screening.

9. For cascade screening, what genes will the patient's first-degree relatives be tested for?

- Only the specific gene with an identified pathogenic variant in the index patient will be tested as part of cascade screening of their first-degree relatives.

IV. Clinical management of FH

10. How does the clinical management of FH differ from that of non-familial hypercholesterolaemia?

- A patient's LDL-C target should be determined based on cardiovascular risk.
- In patients with FH, intensive lipid-lowering therapy should be considered, using maximally-tolerated statin and adding ezetimibe as needed. Further addition of PCSK9 monoclonal antibody or inclisiran for further risk reduction should be based on LDL-C level and clinical need. For further details, please refer to ACE Clinical Guidance "Lipid management: focus on cardiovascular risk"[7] or the guide on FH Genetic Testing and management in Primary Care.
- Evolocumab, a PCSK9 inhibitor, has been included under the MOH Medication Assistance Fund (MAF) since September 2023[8] and will be included in the Healthier SG Medication List (for enhanced subsidies under Healthier SG Chronic Tier) from 2 June 2025. The MAF clinical criteria of evolocumab 140mg/mL solution for injection in prefilled autoinjector are:
  - non-FH or mixed dyslipidaemia, with ASCVD and additional risk factors and LDL-C level above 1.8 mmol/L despite maximal tolerated lipid-lowering therapy (LLT) for at least 12 weeks; or
  - heterozygous FH (HeFH), with ASCVD and LDL-C level above 1.8 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
  - HeFH, without ASCVD, and LDL-C level above 2.6 mmol/L despite maximal tolerated LLT for at least 12 weeks; or
  - homozygous FH (HoFH) with LDL-C level above 1.8 mmol/L despite maximal tolerated statin-lowering therapy for at least 12 weeks.

11. How should patients who are assessed to have clinical FH based on the DLCNS but have a negative FH genetic test result but be managed?

[7] Agency for Care Effectiveness (ACE). Lipid management: focus on cardiovascular risk. ACE Clinical Guidance (ACG), Ministry of Health, Singapore. Available from: go.gov.sg/acg-lipid-management

[8] For more information, physicians may refer to the Technology Guidance from the MOH Drug Advisory Committee published by Agency for Care Effectiveness: https://www.ace-hta.gov.sg/docs/default-source/drug-guidances/pcsk9-inhibitors-for-treating-hypercholesterolaemia.pdf?sfvrsn=a54248fc_4.

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- Patients who undergo genetic testing at the GAC will receive a GAC report which includes treatment recommendations. This includes patients whose genetic test results are negative for known pathogenic variants for FH.
- Physicians are advised to refer to the treatment recommendations within the GAC report when considering further management of their patients.
- A diagnosis of clinical FH based on clinical diagnostic tools for FH such as the DLCNS in the absence of a positive FH genetic test result may be attributed to less common FH-associated genetic mutations, currently unknown genetic associations, or other rare causes (e.g., sitosterolaemia).
- If patients meet the criteria for clinical FH, it is recommended that they are treated as for FH in view of likely elevated risk of atherosclerotic cardiovascular disease.
- Physicians should refer to prevailing national guidelines on the management of patients with hypercholesterolaemia in general.
- Physicians may consider a referral to a specialist for further assessment where necessary.

12. How should management and cascade screening be approached for a patient with a result of "variant of uncertain significance" on the GAC report?

- Recommendations on cascade screening and treatment are included in the GAC report for patients found to have a variant of uncertain significance (VUS).
- Physicians are advised to refer to the treatment recommendations within the GAC report when considering further management of their patients.
- VUS refers to a genetic change or mutation that has been identified, but its clinical significance is currently unclear. Reclassification of the variant may occur over time as more data becomes available.
- A VUS result does not confirm a diagnosis of familial hypercholesterolemia and testing family members for a VUS to guide their medical management is not recommended.
- Patients with a VUS may still be assessed to have clinical FH based on clinical diagnostic tools for FH such as the DLCNS and should be managed accordingly based on their clinical symptoms, family history, and other risk factors.
- Physicians should refer to prevailing guidelines like the ACE Clinical Guidance for lipid management on the management of patients with hypercholesterolaemia in general.
- Physicians may consider a referral to a specialist for further assessment where necessary.

13. Under what circumstances should I refer patients to a specialist for management of hypercholesterolaemia?

- In line with MOH's overall direction, management of hypercholesterolaemia should be anchored in primary care as much as possible (regardless of a FH diagnosis).
- Complex patients may be referred to specialists for further management, at the primary provider's discretion (e.g., if patients are unable to tolerate conventional therapy, or are unable to achieve target LDL-C despite being on maximal

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therapy). Please refer to the guide for on FH Genetic Testing and management in Primary Care for more details.

14. How should hypercholesterolaemia (including FH) be managed in paediatric patients (< 18 years old)?

- The clinical and biochemical criteria (i.e., LDL-C cut-off) to suspect FH in paediatric patients differs from that of adults. Most guidelines adopt different LDL-C cut-offs depending on whether there is family history of high cholesterol, premature ASCVD or known pathogenic variant for FH.
- A referral to a relevant specialist (e.g., paediatric endocrinologist) should be considered, especially if lipid-lowering therapy is warranted.

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