Essentials of a New Clinical Practice Guidance on Familial Hypercholestaemia for Physicians

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.15327

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Introduction

Familial hypercholesterolaemia (FH) is the most common monogenic cause of severe elevation in plasma cholesterol and premature coronary artery disease (CAD). FH is due to gene variants that impair the low-density lipoprotein (LDL)-receptor pathway, thereby resulting in marked increase in plasma LDL-cholesterol from birth. With a prevalence of 1:250 in the community, heterozygous FH (heFH) is more common than other tier 1 genomic conditions, such as hereditary breast and ovarian cancer and Lynch syndrome (1, 2).

Variants causing FH classically occur in the \textit{LDLR}, \textit{APOB} and \textit{PCSK9} genes; the vast majority of individuals with FH have \textit{LDLR} gene variants, with \textit{APOB} and \textit{PCSK9} variants having a lower frequency. FH is an autosomal dominant disorder, meaning that if an individual has one variant in the \textit{LDLR} gene (heFH) their first-degree relatives have a 50% chance of having the condition. If both parents have heFH, there is a 50% chance of their offspring inheriting one variant and having heFH, and a 25% chance of inheriting biallelic variants and having compound heFH (ie. two copies of different variants) or homozygous FH (ie. two copies of the same variant; hoFH) (1, 2). Untreated, heFH on average accelerates the onset of premature CAD by 15 years and hoFH by 30 years. Physical stigmata of FH include arcus cornealis and tendon xanthomata, but these are rarely seen in younger patients with FH (1).

Unless screened for, diagnosed and treated early, the cumulative burden of LDL-cholesterol over a lifetime will result in premature coronary atherosclerosis. Treating FH can have a significant positive impact on public health and healthcare savings (1, 2). Of 100,000 Australians with FH, less than 10% have been identified and over 80% on treatment do not attain LDL-cholesterol targets (2).
The FH Australasia Network Consensus Working Group has developed a new guidance to enhance the care of patients with FH (3). This extract provides key recommendations with their class (CoR) and level of evidence (LoE) (4) (Table 1), particularly for patients with heterozygous FH. The full guidance, including recommendations on homozygous FH, lipoprotein apheresis and organisation of care, is available in *Heart, Lung and Circulation* (3).

**Key recommendations**

*Phenotypic Detection of Index Cases*

**Context and Perspective:**
FH has a population frequency of 1 in 250 and meets all criteria for screening for a condition (1). The detection of index cases is a pre-requisite for cascade testing of close family members. Several approaches, such as selective, opportunistic and universal screening, may be used, but need to be well co-ordinated to be effective (3). Adult index cases may be identified from referrals to cardiology or opportunistically in primary care (1). Universal screening of children has great potential (1), but needs to be further tested in Australia. Alerts on laboratory reports and digital screening of electronic health records may be opportunistically useful for detecting new cases of FH in the community (1, 3).

**Selected Recommendations:**

1. Index cases should be sought by selective screening of adults with premature atherosclerotic cardiovascular disease (ASCVD) and a family history of premature ASCVD and/or hypercholesterolaemia (3, 5). [CoR Strong; LoE High]

2. Opportunistic screening (LDL-cholesterol level >5.0 mmol/L) should be employed for detecting adults (6). [CoR Strong; LoE Moderate]
3. Universal screening (LDL-cholesterol level >3.5 mmol/L) should be considered between 1 to 2 years of age (coinciding with childhood immunisation) to detect children (3, 7). [CoR Moderate; LoE Moderate]

4. The Dutch Lipid Clinic Network (DLCN) criteria (Table 2) should be used to make a phenotypic diagnosis of FH in adults alone (1, 3, 8). [CoR Strong; LoE High]

**Diagnosis and Assessment of Adults**

**Context and Perspective:**
The phenotypic diagnosis of FH is chiefly driven by an elevated LDL-cholesterol level, which is central to the DLCN criteria (Table 1). Genetic testing provides an accurate diagnosis, noting that in 20% of patients with definite phenotypic FH a pathogenic mutation may not be identified (1). Assessment of non-cholesterol risk factors, genetic testing and cardiovascular imaging allows risk re-stratification and improves the precision of treatment (1). It is generally agreed that population cardiovascular risk prediction equations should not be used to assess risk in patients with FH (1, 3).

**Selected Recommendations:**

1. The diagnosis of FH should be made using both phenotypic and genetic criteria, but when genetic testing is not available the diagnosis should be made phenotypically (3, 5). [CoR Strong; LoE High]

2. Genetic testing should be used to confirm the diagnosis of FH, especially if cascade testing is planned (3, 5, 9). [CoR Strong; LoE High]

3. Patients should be risk assessed for the presence of other major ASCVD risk factors (1, 3). [CoR Strong; LoE Moderate]

4. Coronary and carotid artery imaging may be considered for risk stratifying asymptomatic patients (1, 3). [CoR Weak; LoE Moderate]
**Diagnosis and Assessment of Children**

**Context and Perspective:**
In FH the cumulative burden of LDL-cholesterol starts to accrue in childhood (8). The biggest gap in the care of FH is the early detection and treatment of children before ASCVD develops (2). Treating FH from childhood is well supported by good observational studies (1). The phenotypic diagnosis in children is driven by the LDL-cholesterol level, but genetic cascade testing from a parent offers the best diagnosis (8, 9). As in adults, risk stratification enables more rational treatment (1). Consistent with international recommendations, children and adolescents with heterozygous FH should preferably be reviewed by a paediatrician with expertise in lipidology (3, 5, 10, 11).

**Selected Recommendations:**

1. Testing of children should be considered between the ages of 5 and 10 years using phenotypic and genotypic strategies (3, 8, 10). [CoR Moderate; LoE Moderate]

2. A probable diagnosis of FH should be considered in those with (3, 8, 10):
   a. LDL-cholesterol of >5.0 mmol/L (parental history of hypercholesterolaemia or premature ASCVD);
   b. LDL-cholesterol of 4.0 to 5.0 mmol/L (parental history of hypercholesterolaemia or premature ASCVD); or
   c. LDL-cholesterol of >3.5 mmol/L (parent with a pathogenic or likely pathogenic gene variant). [CoR Moderate; LoE Moderate]

3. Genetic testing should be offered to diagnose children after a pathogenic or likely pathogenic gene variant has been identified in a parent or first-degree relative (1, 3, 9, 10). [CoR Strong; LoE Moderate]
4. Children should be risk stratified according to other ASCVD risk factors, family history of premature ASCVD and level of LDL-cholesterol at diagnosis (3, 5, 10, 11).

[CoR Strong; LoE Moderate]

5. In children and adolescents with heterozygous FH, carotid ultrasonography may be considered to assess ASCVD risk (1, 3, 5, 12). [CoR Weak; LoE Moderate]

Genetic Testing

Context and Perspective:
Genetic testing for FH improves diagnosis, ASCVD risk prediction, effectiveness of cascade testing, and adherence to treatment (1, 9). FH is caused by variants in the LDLR, APOB and PCSK9 genes, the majority of pathogenic variants being in the LDLR gene (13). Genetic testing for FH is an MBS item, but testing of potential index cases can only be requested by non-GP specialists (14). Users of genetic testing need upskilling in genomic medicine (15). Accordingly, diagnostic genetic testing of index cases with suspected FH should be requested by a specialist with appropriate skills in the care of patients and families with FH (3, 13-15).

Selected Recommendations:

1. Diagnostic genetic testing and counselling should be offered to all adult index cases with a probable/definite phenotypic diagnosis of FH (1, 3, 9). [CoR Strong; LoE Moderate]

2. Diagnostic genetic testing of children (as probands) should be considered when parents, or first-degree relatives, are unknown or deceased, or as part of universal screening (1, 3, 7). [CoR Moderate; LoE Moderate]

3. Genetic testing should be carried out in an accredited laboratory using standardised methods to detect pathogenic and likely pathogenic gene variants (1, 3, 9, 13). [CoR Strong; LoE High]
4. If a pathogenic, or likely pathogenic, gene variant is not detected, FH should not be excluded (3, 8, 13). [CoR Strong; LoE High]

**Cascade Testing: Risk Notification of Families**

**Context and Perspective:**
Cascade testing involves testing of consenting biological relatives of an individual with confirmed FH (1, 9). Variant specific genetic testing is more cost-effective than phenotypic testing and is now an MBS item that may be requested by GPs (1, 14). Risk notification of family members requires special skills to overcome barriers, such as privacy policy, poor communication in families, health literacy, geographical location and psychological issues (1, 9). Healthcare professionals involved in cascade testing and risk notification of families should receive education in genomic medicine and have basic skills in genetic counselling (3, 9, 13, 15). Co-ordination of cascade testing and risk notification remains a significant challenge (1, 3), and should ideally be co-ordinated by a well-resourced centre (1-3, 9).

**Selected Recommendations:**

1. Cascade testing should be carried out using both a phenotypic and genotypic strategy (Figure 1), but if genetic testing is not available a phenotypic strategy should be used (1-3, 5, 9). [CoR Strong; LoE High]

2. Genetic testing should be employed to screen family members after a pathogenic, or likely pathogenic, gene variant has been identified in the family (1, 3, 9, 13). [CoR Strong; LoE High]

3. When genetic testing is not feasible, the diagnosis of FH in close relatives should be made using age- and gender-specific plasma LDL-cholesterol levels (Table 3) (1-3, 16). [CoR Strong; LoE High]

4. Risk notification of relatives should follow local legislation and institutional guidelines (1-3, 5). [CoR Strong; LoE Low]
5. Pre- and post-test genetic counselling should be offered to at risk family members undergoing cascade testing (1-3, 9, 13). [CoR Strong; LoE High]

**Management of Adults**

Context and Perspective:
Genetic, registry and clinical trial data provide compelling evidence that FH patients be actively treated with lifestyle care and cholesterol lowering drug therapy from an early age (1, 8); other risk factors must be addressed. Shared decision making is the mainstay of adherent therapy. Evidence synthesis supports a 50% reduction in LDL-cholesterol, followed by low absolute targets depending on primary or secondary prevention settings (1, 5). In many patients, attaining very low LDL-cholesterol levels requires sequential treatment with a high potency statin, ezetimibe and a PCSK9 inhibitor (Figure 2) (1, 17, 18), which is now an item on the Public Benefit Schedule that needs to be initiated by a non-GP specialist (19). By contrast to Australia, in New Zealand PCSK9 inhibitors are not reimbursed and are hence only available for patients with FH via a private prescription. Consistent with best practice in preventative medicine, management of adults should employ shared decision making and address patients’ values and health literacy (3, 5).

Selected Recommendations:

1. Patients with FH should be counselled on lifestyle modifications and non-cholesterol risk factors treated (3, 5, 17, 18, 20). [CoR Strong; LoE Moderate]

2. Therapy should initially aim for at least a 50% reduction in LDL-cholesterol (1, 3, 17, 18). [CoR Strong; LoE Moderate], after which the following therapeutic targets should be considered (3, 17, 18, 21) [CoR Moderate; LoE Moderate]:
   a. LDL-cholesterol <2.5 mmol/L (absence of ASCVD or other major ASCVD risk factors);
b. LDL-cholesterol <1.8 mmol/L (imaging evidence of ASCVD alone or other major ASCVD risk factors); or
c. LDL-cholesterol <1.4 mmol/L (presence of clinical ASCVD).

3. Diet and maximally tolerated high potency statins with or without ezetimibe should initially be employed to achieve the above targets (1, 3, 21, 22). [CoR Strong; LoE High]

4. A PCSK9 inhibitor should be employed if targets are not achieved with maximally tolerated statins, ezetimibe and diet (1, 3, 17, 21). [CoR Strong; LoE High]

5. Patients with FH should continue cholesterol-lowering therapies during acute illness, such as respiratory infections, unless specifically contra-indicated (3). [CoR Strong; LoE Low]

6. Plasma hepatic aminotransferases, creatine kinase, glucose and creatinine should be measured before starting and dose titrating statins; creatine kinase should be measured if myalgia is reported; glucose should be monitored with risk of diabetes (checks also apply to children and adolescents) (1, 3, 5). [CoR Strong; LoE Moderate]

7. All women of child-bearing age should be offered pre-pregnancy counselling, with advice on contraception, before starting a statin and this should be reinforced annually (applies also to adolescent girls) (1, 3, 5). [CoR Strong; LoE Moderate]

8. Statins and other systemically absorbed cholesterol lowering drugs should be discontinued 3 months before conception, as well as during pregnancy and breastfeeding (1, 3, 5). [CoR Strong; LoE Moderate]

9. In asymptomatic patients with heterozygous FH, carotid ultrasonography and CTCA may be used for monitoring the efficacy of cholesterol-lowering therapy (1, 3, 12). [CoR Weak; LoE Moderate]
**Management of Children**

Context and Perspective:
Modest and sustained reductions in LDL-cholesterol from early life can have a major effect of mortality due to ASCVD (1, 5, 8). A healthy lifestyle is important, but does not sufficiently lower LDL-cholesterol. A lower potency statin with or without ezetimibe may be required from around the age of 10 years but may be required as early as 2 years in patients with hoFH (1, 5, 8, 10, 11). LDL-cholesterol treatment targets need not be as low as in adults (1, 12); drug safety needs monitoring (1, 8). There is emerging evidence of the safety and efficacy of PCSK9 inhibitors in children (23). Family based clinics, paediatric involvement, shared-decision making, transitional clinics, and strategies for addressing adherence to therapy are essential for enhancing overall care (1, 3, 5, 8, 10, 12).

Selected Recommendations:

1. Patients and families with FH should be counselled on lifestyle modifications, and advice to prevent or correct non-cholesterol risk factors (1, 5, 8, 10, 11, 20). [CoR Strong; LoE Moderate]

2. Initiation of statin treatment should be considered at age 8 to 10 years irrespective of gender; LDL-cholesterol targets in children and adolescents need not be as intensive as in adults (1, 3, 5, 8, 10, 12). [CoR Moderate; LoE Moderate]

3. In children with FH, aged 8 to 10 years on a suitable diet, an LDL-cholesterol treatment target <4.0 mmol/L or a 30-40% reduction in LDL-cholesterol may be considered (1, 3, 8, 10, 11). [CoR Weak; LoE Low]

4. In children older than 10 years on a suitable diet, an LDL-cholesterol treatment target <3.5 mmol/L or a 50% reduction in LDL-cholesterol may be considered (1, 3, 8, 10-12). [CoR Weak; LoE Low]
5. Diet and statin therapy with or without ezetimibe should be employed to achieve the above targets (1, 3, 5, 8, 10, 11). [CoR Strong; LoE High]

6. Statins licenced for use in this age group (pravastatin, fluvastatin, simvastatin) should be employed; ezetimibe is licenced from the age of 10 years and should be used accordingly (2, 3). [CoR Strong; LoE High]

7. The use of atorvastatin and rosuvastatin should be considered according to clinical indications and shared decision making (1, 3). [CoR Moderate, LoE High]

8. Although statins and ezetimibe can be safely used in children, weight, growth, physical and sexual development, and well-being should be monitored (1-3, 8, 10, 11). [CoR Strong; LoE High]

9. Shared care between a paediatrician and a GP should be considered for managing lower complexity patients (3, 5, 6, 8). [CoR Moderate; LoE Low]

Conclusion

This guidance is aligned with an international call to action on FH (24). The recommendations need incorporation into healthcare pathways that meet the needs of the Australian population (1, 2). The MBS item for genetic testing (14) and PBS assisted use of a PCSK9 monoclonal antibody (19) is likely to improve the care of patients with FH over time. Our future challenge is translating the guidance into health policy and high-quality care. Implementation research and practice (24) must be embraced as a priority to increase the impact of this guidance on improving the care of all Australians with or at risk of FH.
Table 1. Classes of recommendations and levels of evidence used in developing the guidance on FH.

<table>
<thead>
<tr>
<th>Classes of Recommendations†</th>
<th>Levels of Evidence‡</th>
</tr>
</thead>
</table>
| Strong recommendation: There is high certainty based on the evidence that the net benefit is substantial  
Wording: should be performed; can be trusted to guide practice | Highly certain about the estimate of effect; further research is unlikely to change our confidence in the estimate of effect  
Bases: Randomised-controlled trials/meta-analyses/systematic reviews/good quality diagnostic studies |
| Moderate recommendation: There is moderate certainty based on the evidence that the net benefit is moderate to substantial, or there is high certainty that the net benefit is moderate  
Wording: should be considered; can be trusted to guide practice in most situations | Moderately certain about the estimate of effect; further research may have an impact on our confidence in the estimate of effect and may change the estimate  
Bases: Good quality clinical or observational studies |
| Weak recommendation: There is at least moderate certainty based on the evidence that there is a small net benefit  
Wording: may be considered; can be trusted to guide practice, but care should be taken in its application | Low certainty about the estimate of effect; further research is likely to have an impact on our confidence in the estimate of effect and is likely to change the estimate  
Bases: Expert opinion based on clinical experience or argument from first principles* |

†This system was based on the American Heart Association/American College of Cardiology (25) and the National Lipid Association (26) cholesterol guidelines.

‡This system was based on the American Heart Association/American College of Cardiology (25) and the National Lipid Association (26) cholesterol guidelines, and adapted from the original GRADE system of evidence rating (4), which is in turn endorsed by the National Health and Medical Research Council Guidelines for Guidelines (27).
Table 2. The Dutch Lipid Clinic Network criteria for making the phenotypic diagnosis of familial hypercholesterolaemia in adult index cases (1-3). For online use, please access the FH Australasia Network calculator at https://www.athero.org.au/fh/calculator/. These criteria should not be used to diagnose FH in children or adolescents (1, 3, 8).

<table>
<thead>
<tr>
<th>Criteria*</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td><strong>Section 1: Family history</strong></td>
<td></td>
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<tr>
<td>First degree relative with known premature coronary and/or vascular disease (men aged &lt;55 years, women aged &lt;60 years) OR First degree relative with known LDL-cholesterol above the 95th percentile for age and gender</td>
<td>1</td>
</tr>
<tr>
<td>First degree relative with tendinous xanthomata and/or arcus cornealis OR Children aged &lt;18 years with LDL-cholesterol above the 95th percentile for age and gender</td>
<td>2</td>
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<tr>
<td><strong>Section 2: Clinical history</strong></td>
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<tr>
<td>Patients with premature coronary artery disease (men aged &lt;55 years, women aged &lt;60 years)</td>
<td>2</td>
</tr>
<tr>
<td>Patients with premature cerebral or peripheral vascular disease (men aged &lt;55 years, women aged &lt;60 years)</td>
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<tr>
<td><strong>Section 3: Physical examination</strong></td>
<td></td>
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<tr>
<td>Tendinous xanthomata</td>
<td>6</td>
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<tr>
<td>Arcus cornealis before 45 years of age</td>
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<tr>
<td><strong>Section 3: Biochemical results</strong></td>
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<tr>
<td>LDL-cholesterol (mmol/L)†</td>
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<td>LDL-cholesterol 6.5–8.4</td>
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<td>LDL-cholesterol 5.0–6.4</td>
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<td>LDL-cholesterol 4.0–4.9</td>
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*Note that only the highest score in each section is chosen to add up to the total score, to a maximum of 18.

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<th>Diagnosis</th>
<th>Total Score</th>
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<tr>
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<td>Possible FH</td>
<td>3-5</td>
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<tr>
<td>Unlikely FH</td>
<td>&lt;3</td>
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†If pre-treatment LDL-cholesterol is not available, use the FH Australasia Network’s online calculator (https://www.athero.org.au/fh/calculator/) to derive the LDL-cholesterol by adjusting value for cholesterol-lowering medication.
Figure 1. Scheme for cascade testing of biological relatives of an index case with confirmed familial hypercholesterolaemia.

^Consistent with relevant local legislation and institutional guidelines

Table 3. Age-dependent plasma LDL-cholesterol concentrations and thresholds (mmol/L) for making a diagnosis of FH during cascade testing in (a) male and (b) female first-degree relatives of an index case with FH. Adapted from Starr et al 2008 (16).

(a) Male

<table>
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<th>25 to 34</th>
<th>35 to 44</th>
<th>45 to 54</th>
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(b) Female

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Colour | Likelihood of FH
---|-------------------
Red     | Likely
Yellow  | Uncertain
Blue    | Unlikely
Figure 2. Sequence of therapy for adults with familial hypercholesterolaemia (FH). Most patients with heterozygous FH can be well controlled with a two- or three- drug combination; statin intolerant patients may be treated with ezetimibe and a PCSK9 inhibitor. Complex therapy regimens will usually apply to patients with homozygous FH (1, 5, 21), which may include children and adolescents. LDL-cholesterol targets are based on primary or secondary prevention settings (1); patients should be on at least 3 months of therapy and above the targets before proceeding to next step. *For targets, see Management of Adults in text. Adapted from Pang et al 2020 (2).

After diet, lifestyle advice and shared decision making (use at every stage of therapy), use high-intensity statin therapy aiming for a 50% reduction in LDL-cholesterol

If LDL-cholesterol is above guideline recommended target*, proceed to two-drug combination

High-intensity statin + Ezetimibe

If LDL-cholesterol is above guideline recommended target*, proceed to three-drug combination

High-intensity statin + Ezetimibe + PCSK9 inhibitor

If LDL-cholesterol is above guideline recommended target*, proceed to complex therapy regimen

High-intensity statin + Ezetimibe + PCSK9 inhibitor + LDL apheresis and/or compassionate use of novel drugs (eg. lomitapide, evinacumab)
Appendix

All tables and figures are reprinted by kind permission of Heart, Lung & Circulation (2, 3).

Endorsements

The full guidance (3) has been endorsed by the Australian Atherosclerosis Society, Cardiac Society of Australia and New Zealand, National Heart Foundation (Australia), Australian Cardiovascular Alliance, Human Genetics Society of Australasia, European Atherosclerosis Society, International Atherosclerosis Society, FH Foundation, Heart UK, Asian-Pacific Society of Atherosclerosis and Vascular Disease, National Lipid Association (US) and the American Society of Preventive Cardiology.

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References


Abstract

Familial hypercholesterolaemia (FH) is a common, heritable and preventable cause of premature coronary artery disease. New clinical practice recommendations are presented to assist practitioners in enhancing the care of all patients with FH. Core recommendations are made on the detection, diagnosis, assessment and management of adults, children and adolescents with FH. Management is underpinned by the precepts of risk stratification, adherence to healthy lifestyles, treatment of non-cholesterol risk factors, and appropriate use of low-density lipoprotein (LDL)-cholesterol lowering therapies, including statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. The recommendations need to be utilised using judicious clinical judgement and shared decision making with patients and families. New government funded schemes for genetic testing and use of PCSK9 inhibitors, as well as the National Health Genomics Policy Framework, will enable adoption of the recommendations. A comprehensive implementation science and practice strategy is, however, required to ensure that the guidance translates into benefit for all families with FH.
Essentials of a New Clinical Practice Guidance on Familial Hypercholesterolaemia for Physicians

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In accordance with the policies of the Royal Australasian College of Physicians, the Internal Medicine Journal requires that ALL Authors advise the Corresponding Author of any potential financial or other conflict of interest before a paper is published. Once these requirements have been accepted by the Corresponding Author, he/she can complete, sign and submit (one only) ICMJE form on behalf of ALL the Authors. This form is in four parts:

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2. Surname (Last Name)  
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4. Are you the corresponding author?  
   [ ] Yes  [ ] No

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### The Work Under Consideration for Publication

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<th>Money Paid to You</th>
<th>Money to Your Institution</th>
<th>Name of Entity</th>
<th>Comments**</th>
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<td>5. Payment for writing or reviewing the manuscript</td>
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<td>6. Provision of writing assistance, medicines, equipment, or administrative support</td>
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## Section 3. Relevant financial activities outside the submitted work.

Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the "Add +" box. You should report relationships that were present during the 36 months prior to submission.

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### Relevant financial activities outside the submitted work

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<th>Type of Relationship (in alphabetical order)</th>
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<th>Money to Your Institution*</th>
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<td>Sanofi, Amgen, Novartis, Aronheim</td>
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<td>6. Payment for lectures including service on speakers bureaus</td>
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<td>7. Payment for manuscript preparation</td>
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<th>Money to Your Institution*</th>
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<td>13. Other (err on the side of full disclosure)</td>
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