Commentary

A Model of Care for Familial Hypercholesterolaemia: Key Role for Clinical Biochemistry

*Gerald F Watts,[1] David R Sullivan,[2] Frank M van Bockxmeer,[3] Nicola Poplawski,[4] Ian Hamilton-Craig,[5] Peter M Clifton,[6] Richard C O'Brien,[7] Peter M George,[8] John R Burnett,[9] for the Familial Hypercholesterolaemia Australasia Network

[1]Lipid Disorders Clinic, Metabolic Research Centre and Department of Internal Medicine, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia; [2]Department of Biochemistry and Lipid Clinic, Royal Prince Alfred Hospital, University of Sydney, NSW, Australia; [3]Core Clinical Pathology & Biochemistry, PathWest Laboratory Medicine WA, Royal Perth Hospital, University of Western Australia; [4]South Australia Clinical Genetics Service, Genetics and Molecular Pathology Directorate, Women's & Children's Hospital, Adelaide, SA, Australia; [5]Preventive Cardiology and Lipid Clinic, Gold Coast Hospital, Griffith University, Qld, Australia; [6]Baker IDI Heart and Diabetes Institute, Adelaide, SA, Australia; [7]Department of Medicine, Diabetes and Endocrinology, Austin Hospital, University of Melbourne, Melbourne, Vic., Australia; [8]Biochemistry and Pathology, Canterbury Health Laboratories, Lipid Clinic, Christchurch Hospital, University of Otago, Christchurch, New Zealand; [9]Core Clinical Pathology & Biochemistry, PathWest Laboratory Medicine WA, Lipid Disorders Clinic, Royal Perth Hospital, University of Western Australia.
*For correspondence: Winthrop Professor Gerald F Watts, gerald.watts@uwa.edu.au

Abstract

Familial hypercholesterolaemia (FH) is a dominantly inherited disorder present from birth that causes marked elevation in plasma low-density lipoprotein (LDL) cholesterol concentrations and premature coronary heart disease. There are at least 45,000 people with FH in Australia and New Zealand, but most remain unrecognised and those diagnosed remain inadequately treated. To bridge this gap in coronary prevention the FH Australasia Network has developed a model of care for FH. An executive summary of the model of care is presented, with a commentary on its recommendations and the key role of the clinical biochemistry laboratory.

Context

Familial hypercholesterolaemia (FH) is a condition that should be familiar to all health professionals involved in preventive medicine, as well as to laboratories that support these services. FH is the most common and serious monogenic disorder of lipid metabolism (OMIM #143890) that leads to premature coronary heart disease (CHD) due to accelerated atherosclerosis.[1,2] If untreated, approximately half the men and women with FH develop CHD by age 50 years and 60 years, respectively.[3] At least 10% of people with premature CHD (i.e. below 60 years of age) may have FH. [4,5]

FH is an autosomal co-dominantly inherited disorder caused primarily by mutations in the gene that encodes the LDL-receptor (*LDLR*) on the short arm of chromosome 19;[1,6] rarer mutations in the *APOB* and *PCSK9* genes have similar functional consequences. In FH there is a classical defect in the LDL-receptor pathway leading to decreased clearance of LDL-cholesterol from plasma,[6] with consequent increase in the concentration of total and LDL-cholesterol. The prevalence of FH is estimated to be at least 1 in 500 in the general population, being much higher in communities subject to a 'founder gene effect'.[3] The most cost-effective approach for detecting FH is to identify index cases first and then cascade screen family members (i.e. tracing of family members) for the condition.[7] The therapeutic use of statins in routine clinical practice since about 1990 has markedly improved the prognosis of patients diagnosed with FH.[8-10]

However, in spite of major advances in scientific and clinical knowledge about the condition, most cases of FH remain undetected or inadequately treated in our community.[4,11,12] To meet this demand, several guidelines on the detection and management of FH have been published.[13-17] The most recent and comprehensive is that provided by the FH Australasia Network.[17] This set of guidelines, developed from

an Australian and New Zealand perspective, constitutes what is known as a 'model of care', defined as an overarching system, based on theoretical, experiential and evidence-based standards, for provision of highest quality health care services for FH. We provide the executive summary of the model of care and a commentary that refers to the potential role of the clinical biochemistry laboratory. The parent article should be consulted for further details,[17] including algorithms that define the clinical and laboratory pathways and grades for the recommendations.

Australasian Model of Care for Familial Hypercholesterolaemia
The following recommendations have been republished from Watts GF, et al. Familial hypercholesterolaemia: A model of care for Australasia. Atheroscler Suppl 2011;12:221-63, with permission from Elsevier.

The recommendations are graded 'A', 'B' or 'C'. These grades were reached by full consensus of the steering committee.[17] An 'A' grade indicates that data/opinion supports that the recommendation can be trusted to guide practice, a 'B' grade indicates that the recommendation can be trusted to guide practice in most situations, and a 'C' grade indicates that the recommendation may be used to guide practice, but care should be taken in the application.[17]

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1. Models of Care and Components of Service
1.1 Models of care for FH should focus on detecting, diagnosing, assessing and managing index cases, as well as on risk notification and cascade screening of family members. (A)
1.2 Adults and children/adolescents will require different models of care. (A)
1.3 All services need to be integrated across several specialties and incorporated into primary care. (A)
1.4 Good clinical governance, teaching and training programs, and family support groups are integral to all models of care. (A)

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2. Identifying Index Cases
2.1 Index cases of FH should be sought amongst adults with premature cardiovascular disease in primary and secondary care settings. (A)
2.2 In adults a simple clinical tool based on the Dutch Lipid Clinic Network Score should be used. (A)
2.3 All patients with possible-to-definite FH should be referred to a lipid disorders clinic for more detailed assessment and institution of cascade screening. (A)

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3. Clinical Assessment and Management Allocation of Adults
3.1 Secondary causes of hypercholesterolaemia should first be excluded. (A)
3.2 The diagnosis of FH should be made using both phenotypic and genetic testing. (A)
3.3 Patients should be stratified into risk categories according to presence of cardiovascular risk factors and personal history of cardiovascular disease. (A)
3.4 Risk stratification should guide the intensity of medical management. (A)

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4. Clinical Assessment and Management Allocation of the Young
4.1 Children (age 5 years and above) and adolescents should be tested for FH after the diagnosis of FH has been made in a parent. (A)
4.2 Secondary causes of hypercholesterolaemia should first be excluded. (A)
4.3 With rare exceptions, children and adolescents should only be genetically tested for FH after a mutation has been identified in a parent or first degree relative. (A)
4.4 Age- and gender-specific plasma LDL-cholesterol concentration thresholds should be used to make the phenotypic diagnosis, with an LDL-cholesterol of 5.0 mmol/L or above indicating highly probable/definite FH; two fasting lipid profiles are recommended. (B)
4.5 Patients should be stratified into risk categories according to age, presence of other cardiovascular risk factors, prematurity of family history of cardiovascular disease and the level of hypercholesterolaemia at diagnosis. (A)
4.6 Risk stratification should guide the intensity of medical management. (A)

5. *Management of FH in Adults*

5.1 All adult patients with FH must receive advice on lifestyle modifications and all non-lipid risk factors must be addressed. (A)

5.2 Plasma LDL-cholesterol targets for routine, enhanced and intensive management should be <4 mmol/L, <3 mmol/L, <2 mmol/L, respectively. (C)

5.3 Achieving these targets will require a fat-modified diet, plant sterols (or stanols) and a statin with or without ezetimibe. (A)

5.4 Niacin, resins and a fibrate may be required with more intensive strategies. (A)

5.5 Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured before starting pharmacotherapy. All patients on pharmacotherapy, particularly statins, should have hepatic aminotransferases monitored; creatine kinase should only be measured when musculoskeletal symptoms are reported; creatinine should be monitored in those with kidney disease. (A)

5.6 All women with FH of child-bearing age should have pre-pregnancy counselling. (A)

5.7 Statins and other systemically absorbed lipid regulating agents should be discontinued 3 months before conception and during pregnancy and breast feeding in women with FH. (A)

5.8 Non-invasive testing for coronary heart disease and atherosclerosis should be considered in patients undergoing standard and enhanced treatment, with a step-up in treatment considered if there is evidence of progression of disease. Non-invasive testing for atherosclerosis need not be carried out more frequently than every two years. (C)

5.9 Patients receiving standard or enhanced management should be reviewed every 6 to 12 months, and those receiving intensive management should be reviewed according to clinical context, with appropriate interval assessment of cardiac function and referral to cardiology. (B)

6. *Management of FH in the Young*

6.1 Patients must receive advice on lifestyle modifications and non-lipid risk factors must be addressed. Effective anti-smoking advice is mandatory. (A)

6.2 Lowest risk patients should be treated expectantly with a fat-modified diet with or without plant sterols (or stanols), with statins considered after the age of 10 years in boys and after the menarche in girls. (B)

6.3 Plasma LDL-cholesterol targets for intermediate and high risk patients should be <4 mmol/L and <3 mmol/L, respectively. (C)

6.4 Reaching these targets requires a fat-modified diet, plant sterols (or stanols) and a statin with or without ezetimibe or a bile acid sequestrant. (A)

6.5 The preferred statins for initiating therapy are those that are licensed for clinical use in this age group; in Australia these are pravastatin, fluvastatin or simvastatin, but other statins may be prescribed according to clinical indications. (C)

6.6 Weight, growth, physical and sexual development, and well-being should be reviewed regularly in all patients. (B)

6.7 Plasma levels of hepatic aminotransferases, creatine kinase and creatinine should be measured before starting pharmacotherapy. All patients receiving statins should have hepatic aminotransferases monitored; creatine kinase should be measured when musculoskeletal symptoms are reported; creatinine should be monitored in those with kidney disease. (A)

6.8 Carotid artery ultrasonography should be considered for assessing intima-medial thickness and presence and progression of plaques; this may guide the intensity of medical management. Ultrasonography need not be carried out more frequently than every 2 years. (C)

6.9 Consideration should be given to managing children and adults with FH from the same family in a family-centred clinic. (B)

7. *LDL-apheresis*

7.1 LDL-apheresis should be considered in patients with homozygous or compound heterozygous FH. (A)

7.2 LDL-apheresis should be considered in patients with heterozygous FH with documented coronary heart disease who are refractory to or cannot tolerate cholesterol lowering medication. (A)

7.3 LDL-apheresis should be considered in children with homozygous or compound heterozygous FH by the age of 5 years, particularly if the plasma cholesterol concentration remains at 9 mmol/L or above on medication. (A)

7.4 LDL-apheresis should be carried out in close collaboration with a centre experienced in apheresis, such as a transfusion medicine service. (A)

7.5 The efficacy, tolerability and safety of LDL-apheresis must be reviewed after each treatment. (A)

7.6 The effect of LDL-apheresis on progression of atherosclerosis should be monitored with echocardiography (aortic valve and root), carotid ultrasonography and/or exercise stress testing. (B)

8. Cascade Screening: Risk Notification and Genetic/Phenotypic Testing of Families

8.1 Notification of relatives at risk of FH should not be instituted without the consent of the index case, with the exception noted below in recommendation 8.3. (A)

8.2 If no consent is given by the index case, rapport should continue to be built and consideration given to referral for counselling. (B)

8.3 Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for this breach of confidentiality in the relevant jurisdiction. (C)

8.4 Commonwealth legislation, local state legislation, NHMRC guidelines and local health service protocols about disclosure of medical information without consent should be consulted. (A)

8.5 A proactive approach that respects the principles of privacy and autonomy is required. (A)

8.6 All material sent to relatives and the telephone approach should be clear, comprehensible and not cause alarm. General and specific modes of communication should be used. (A)

8.7 Cascade screening should ideally be carried out as a formal collaborative process between lipid disorders and clinical genetics services. It should also involve close communication and liaison with primary care physicians and employ a user-friendly family based data management system. (A)

8.8 Pre-testing counselling should be offered to at risk family members of an index case prior to phenotypic or genetic testing. (A)

8.9 If no consent/assent for genetic testing is obtained, phenotypic testing for FH should be offered. (A)

8.10 If genetic testing detects the family mutation, a definitive diagnosis of FH can be made in the tested individual particularly when the phenotype also suggests FH. (A)

8.11 If genetic testing does not detect the family mutation, the diagnosis of FH can be excluded, except when the clinical phenotype is highly suggestive of FH. (A)

9. Genetic Testing for FH: Laboratory Approach

9.1 Genetic testing for FH should be offered to all 'index cases' who have a phenotypic diagnosis of FH (e.g. by Dutch Lipid Clinic Network Score). (A)

9.2 When the phenotypic diagnosis of FH is unlikely (e.g. by Dutch Lipid Clinic Network Score), genetic testing of the 'index case' need not be carried out. (C)

9.3 Genetic testing for FH must be carried out in an accredited laboratory. (A)

9.4 When searching for a mutation in an 'index case', genetic testing may be carried out initially using commercial chip or kit technology. (B)

9.5 All abnormal genetic test results by chip or kit technology should be confirmed using a different validated method. (A)

9.6 When the phenotypic diagnosis of FH is definite or probable (e.g. by Dutch Lipid Clinic Network Score), but no genetic variant is detected by methods that target specific mutations, comprehensive exon by exon sequencing is recommended. (A)

9.7 If genetic testing detects a variant, the laboratory report should include an assessment of its significance, and clearly indicate whether the variant is a pathogenic mutation, a previously reported variant of uncertain significance, a novel variant of uncertain significance or a benign (normal) variant. (A)

9.8 If the genetic testing protocol does not detect a mutation, the laboratory report should include a caveat that the result does not exclude FH due to undetected mutations or mutations in untested genes, particularly if the clinical phenotype is strongly suggestive of FH. (A)

Commentary

The recommendations of this model of care for FH are generally congruent with other guidelines in respect of the methods for case detection and cascade screening, the approach to children and adolescents, use of lifestyle and drug-treatment strategies and indications for LDL-apheresis.[13-16,18,19] Almost all the recommendations are graded at the A or B levels, with C level recommendations pertaining to treatment targets in children, use of carotid ultrasonography, risk notification of relatives without consent of the index case, and to the genetic screening of index cases with an unlikely phenotypic diagnosis of FH.[17]

By contrast to recent US guidelines,[15] we do not recommend universal screening for hypercholesterolaemia in children aged 9 to 11 years because the practicability and cost-effectiveness of this approach are unclear.[17,19] Targeted screening of potential index cases in coronary care units and primary care, followed by a vigorous, but ethically regulated family tracing strategy is the prime recommendation.[5,17] The choice of phenotypic tools for diagnosing adult FH is from the MED-PED,[20] Simon Broome[13] and Dutch Lipid Clinic Network criteria.[22] While these are considered equally useful in predicting FH mutations in adults,[19] we consider that the Dutch Lipid Clinic Network Score, which estimates a numerical probability of having FH based on the personal and family history of premature CHD and hypercholesterolaemia and on clinical stigmata, as the most sensitive approach upon which a decision to carry out a DNA test may be made.[17]

We stress the value of genetic testing for FH within families following the detection of a pathogenic mutation in an index case,[3,13,17,22] but concur with other recommendations that a combined phenotypic and genetic testing strategy offers the most effective approach for detecting new cases.[13] The cost-effectiveness of cascade screening compared with other methods, such as universal screening, has been well demonstrated in FH.[7,13] Our laboratory protocol is based on serial tests for the detection of genetic variants in individuals stratified by the *a priori* likelihood of carrying a causative mutation based on the Dutch Lipid Clinic Network Score.[17] Individuals with at least a possible phenotypic diagnosis of FH are screened using commercial DNA diagnostic methods, Multiplex-Ligation Probe Amplification (for large insertions/deletions, duplications and copy number variations) and exon-by-exon sequence analysis has practical merit and novelty value.[17] However, it is likely to be superseded in the near future by rapid and inexpensive methods of whole exome and possibly whole genome sequencing that could be more universally applied in screening for FH.[23,24] The relative yield and cost-effectiveness of a selective compared with a less selective approaches to DNA testing of potential index cases of FH at a population level needs evaluation.

The Australasian guidelines uniquely underscore the value of non-invasive imaging for atherosclerosis in assessing and managing FH patients without clinically demonstrable coronary disease,[17,25] but caution that care should be taken in its application (Level C recommendation) and stress the importance of employing a fully credentialled vascular imaging service.[17] A universally agreed target treatment level for heterozygous patients is at least a 40% reduction in plasma LDL-cholesterol concentration.[13-17,22] The Australasian model of care specifies targets of <4.0, <3.0 and <2.0 mmol/L for patients with lowest, intermediate and highest risk, respectively,[17] recognising that CHD risk in FH is variably affected by factors beyond hypercholesterolaemia.

Lifestyle changes are underscored by all guidelines.[13-17,22] Statins with or without other agents are required to meet these targets and careful pre-treatment checks on liver and muscle enzymes are required, with regular monitoring of plasma aminotransferases, and if myalgia is reported, checking of plasma creatine kinase.[17,22] The safety of statins in children is reaffirmed and their use in those over the age of 10 years advised.[16,17,22,26] Uniform recommendations are given for avoiding statins in women with FH during (or planning) pregnancy and lactation, and choosing low oestrogen oral or progesterone-only oral contraceptives, with barrier methods preferred.[17,27]

The Australasian model of care also provides recommendations concerning integration of services, administrative and information technology requirements, clinical governance, teaching and credentialling and establishing a family support group.[17]

Role of Clinical Biochemistry

So what is the role of the clinical biochemistry laboratory and chemical pathologists? The clinical biochemistry laboratory is integral to all levels of service provision.[17,22] Besides routine testing for secondary causes of hypercholesterolaemia and monitoring of the effectiveness and safety of drug therapy, the laboratory should offer more specialized tests to aid risk assessment (e.g. lipoprotein(a)), and to guide intensity of therapy (e.g. apoB in patients with hypertriglyceridaemia).[28,29] In some instances, genetic testing for FH may be offered within clinical biochemistry by a subspecialty laboratory that complies with the requirements of the National Pathology Accreditation Advisory Council and the National Association of Testing Authorities.[17]

The biochemistry laboratory is also ideally placed to assist with screening for FH in, for example, general practice and coronary care, by including an effective interpretive comment on laboratory reports that alert the requestor to

the possibility of FH.[17,28] Interpretive comments could be guided by the identification of an isolated increase in plasma LDL-cholesterol concentration, the degree of elevation in LDL-cholesterol, detection of hypercholesterolaemia in the young, and exclusion of laboratory evidence of hypercholesterolaemia (hypothyroidism, nephrosis).[28] The chemical pathologist can offer additional advice on selection of additional tests[28,29] and possible referral to a specialised clinic through the family doctor. In the most frank cases of FH direct verbal communication with requestors is likely to be more effective than interpretive commenting alone. Improved communication between laboratories and requesting practitioners can potentially close a major gap in the detection and management of FH.[28]

The evolution of clinical lipidology as a specialty has allowed an opportunity for a suitably credentialled chemical pathologist to offer consultative services in FH,[30] providing an ideal channel of communication between the referring clinician and the laboratory. Training in metabolic medicine affords similar opportunities.[31] The future may herald additional new roles for clinical biochemistry in the care of patients with FH in testing the pharmacogenomic response to lipid-regulating drug therapy.

Conclusions

The present model of care for FH is intended primarily for lipid disorder clinics in tertiary centres. A model of care for general practice needs to be developed. Biochemistry laboratories and chemical pathologists can play a crucial role in supporting services across the continuum of care. Publishing a model of care for FH that meets the requirements of several stakeholders is important, but effectively implementing and ensuring the uptake of these recommendations in routine clinical practice is another, a challenge well emphasised by recent reports from several countries.[32,33] Implementation and effective sustainability, both underpinned by appropriate financing by governments, private sector and other sources, is where the ultimate challenge lies for services for FH and related genetic dyslipidaemias.

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