Table 1 A review of coexisting CHL and NLPHL cases

Case	Type	Age/ Sex	First Bx site/Dx	BM	Initial stage	Therapy	Response	Second Bx site/Dx	Time interval (years)	Clonal relationship	LMP/ EBER	Status/ follow up (years)	Reference
1	Metachronous	21/M	LN: NLPHL	N/A	N/A	N/A	N/A	Spleen: CHL, MC	5	ND	N/A	Alive/6	4
2	Metachronous	17/M	LN: NLPHL	Neg	IA	Roentgen therapy	N/A	LN (same site): CHL,MC	17	ND	N/A	Dead/19	4
3	Metachronous	10/M	LN: CHL, MC	Neg	IA/IB	XRT+Chemo	CR	LN (diff. site) NLPHL	18	ND	LMP/—	N/A	2
4	Metachronous	30/M	LN: CHL, NS	Neg	IIIAS	Auto BMT	N/A	LN (same site): NLPHL	10	ND	LMP/—	Dead/11	2
5	Metachronous	22/M	LN: CHL, NS	Neg	IIIAS	ABVD	PR	LN (diff. site): NLPHL	5	ND	LMP/—	N/A	2
6	Metachronous	27/M	LN: NLPHL	N/A	N/A	Adriamycin, vinblastine sulfate, VP16	PR	LN (same site): CHL,NS	3	ND	LMP/—	N/A	2
7	Composite	22/M	LN: CHL,MC + NLPHL	Neg	IA/IB	XRT	CR	NA	NA	ND	ND	N/A	2
8	Synchronous	24/M	Thymic mass: CHL,NS Parotid mass: NLPHL	Neg	N/A	N/A	N/A	NA	NA	Clonally related	EBER/ both —	N/A	3
9	Composite	48/M	LN:CHL,MC + NLPHL	Neg	IIIA	ABVD+ XRT+ BEACOPP	CR	NA	NA	Clonally related	EBER CHL/+ NLPHL/ —	Alive/1.8	5
10	Metachronous	14/M	LN: CHL, NS	Neg	IIIAS	ABVE-PC+ XRT	CR	LN (diff. site) NLPHL	4.3	Clonally related	EBER/ both —	Alive/7.8	Current case

ABVD, adriamycin, bleomycin, vinblastine sulfate, dacarbazine; ABVE-PC, adriamycin, bleomycin, vincristine sulfate, etoposide, prednisone and cyclophosphamide; BEACOPP, cyclophosphamide, doxorubicin, etoposide phosphate, naltrexone, vincristine, bleomycin; BMT, bone marrow transplant; Bx, biopsy; Chemo, chemotherapy; CHL, classic Hodgkin lymphoma; CR, complete remission; diff, different; Dx, diagnosis; EBER, EBV-encoded RNA; F, female; LMP, latent membrane protein; LN, lymph node; M, male; MC, mixed-cellularity; NA, not applicable; N/A, not available; ND, not done; Neg, negative; NLPHL, nodular lymphocyte predominant Hodgkin lymphoma; NS, nodular sclerosis; PR, partial remission; XRT, radiotherapy.

recurrent disease, biopsy of the relapsed lesion is essential for diagnosis and treatment purposes.

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The lipid profile in children prior to isotretinoin therapy: an opportunity to detect familial hypercholesterolaemia

Sir,

Familial hypercholesterolaemia (FH) is an autosomal dominant disorder of low density lipoprotein (LDL) catabolism associated with elevated LDL cholesterol and premature atherosclerotic coronary artery disease (CAD).¹ FH has been shown to be more prevalent than previously thought, occurring in ~1:250 people.^{2,3} However, the vast majority of individuals with FH are undiagnosed and often under treated.¹ A recent study demonstrated that initiation of statin therapy in childhood was associated with reduced coronary artery disease.⁴ FH is predominantly caused by variants in the LDL receptor (*LDLR*), apolipoprotein B (*APOB*) or proprotein

convertase subtilisin/kexin type 9 (*PCSK9*) genes.¹ There are multiple diagnostic criteria for FH, with the Dutch Lipid Clinic Network Criteria preferred for Australia, although there is no international consensus.⁵

An international consensus guideline on optimising the detection and management of children and adolescents with FH has been published by the European Atherosclerosis Society (EAS).⁶ This report highlighted the need to detect and treat children and adolescents with FH and proposed simple LDL cholesterol based criteria to alert clinicians when an individual is at risk of FH. A child with an LDL cholesterol ≥ 5.0 mmol/L on two successive occasions indicates probable FH, after excluding secondary causes of hypercholesterolaemia. FH is very likely in a child with an LDL cholesterol ≥ 4.0 mmol/L, if they have a parent with a history of elevated cholesterol or premature CAD. An LDL cholesterol ≥ 3.5 mmol/L in a child of a parent with genetically confirmed FH indicates probable FH. However, most adults with FH are currently undiagnosed, so identifying children may allow opportunistic reverse cascade testing of their parents, as illustrated in the following case.

A 16-year-old girl was referred to a Lipid Disorders Clinic having been found to have significant hypercholesterolaemia on routine biochemical testing prior to commencing isotretinoin therapy for acne. A fasting lipid profile showed a total cholesterol of 8.0 mmol/L, HDL cholesterol 1.6 mmol/L, triglyceride 1.8 mmol/L, and LDL cholesterol 5.6 mmol/L. The only significant past medical history was asthma and her medications included a salbutamol inhaler, fish oils 750 mg per day, and Diane 35 (oral contraceptive pill). Her mother was known to have hypercholesterolaemia, but was not on lipid lowering therapy and her maternal grandparents were alive in their sixties. There was no family history of premature CAD. On physical examination, she appeared in good health, with a body mass index of 21 kg/m² and BP 104/61 mmHg. There were no peripheral stigmata of lipid disorders. A cardiovascular respiratory examination was unremarkable. Based on a Dutch Lipid Clinic Network Criteria score of four, she was given a diagnosis of possible FH. Subsequent analysis of the *LDLR* gene revealed that both she and her mother were heterozygous for a missense variant c.661G>A (p.D221N) in exon 4, which occurs within repeat 5 of the ligand binding domain and which was predicted to be pathogenic.

As a result of this case, we sought to explore the potential role dermatologists could play in the opportunistic detection of children with FH using the LDL cholesterol results and clinical information on laboratory request forms for individuals aged <18 years from a community laboratory. The population consisted of 84,823 individuals who had plasma lipid profiles measured between 1 May 2010 and 31 April 2011 at St John of God Pathology in Western Australia. The demographics of the population have been previously described; their mean age was 56 ± 15 years with a mean LDL cholesterol of 3.1 mmol/L.⁷

There were 444 children aged <18 years in this population; their mean age was 14.9 ± 2.4 years, 211 (47.5%) were male, with a mean total cholesterol of 4.21 ± 0.93 mmol/L, LDL cholesterol of 2.46 ± 0.80 mmol/L, and triglycerides of 1.02 ± 0.62 mmol/L. The distribution of LDL cholesterol results is shown in Fig. 1. There were 43 (9.7%) children with an LDL cholesterol ≥ 3.5 mmol/L, 18 (4.1%) ≥ 4.0 mmol/L, and two (0.5%) ≥ 5.0 mmol/L.

Fig. 1 Distribution of plasma LDL cholesterol concentrations in 444 children <18 years over a one year period in a community laboratory.

There were 96 (21.6%) lipid profiles requested by dermatologists; 64 males and 32 females, mean age 15.5 years (range 12–17). In these 96 individuals, the mean total cholesterol was 4.0 ± 0.9 mmol/L, LDL cholesterol 2.3 ± 0.7 mmol/L (maximum 4.5 mmol/L) and triglycerides 1.0 ± 0.5 mmol/L (maximum 2.7 mmol/L). Nine (9.4%) children had an LDL cholesterol ≥ 3.5 mmol/L, and two (2.1%) ≥ 4.0 mmol/L. Clinical information was provided on 58 (60.4%) requests; 53 (91.4%) stating 'isotretinoin' or 'acne'. 'Isotretinoin' or 'acne' was mentioned on five (1.4%) of the remaining 348 lipid profiles not requested by a dermatologist.

Dermatologists already detect some children with homozygous FH, who usually have an LDL cholesterol >13 mmol/L and may have coronary, aortic and valvular atherosclerosis and events in their early teenage years, and who present for investigation of cutaneous xanthomata.⁶ The Australasian College of Dermatologists recommend lipid testing prior to and after starting isotretinoin,⁸ as this treatment can lead to elevations of triglyceride and cholesterol in some patients,⁹ who are then more likely to have dyslipidaemia and the metabolic syndrome later in life.¹⁰ Dermatologists order a significant number of lipid profiles in children and adolescents.

The case and data presented suggest that dermatologists could play an important role in detecting FH and help close this gap in preventative cardiology. Childhood is the optimal time to differentiate individuals with FH using LDL cholesterol concentrations, and, if treated, can lead to the greatest reductions in lifetime LDL cholesterol exposure. Therefore, there is potential to significantly increase the detection of FH in the community through collaboration between the chemical pathologist and dermatologist, especially if combined with testing the parents (reverse cascade screening),⁵ and other first degree family members.

The community laboratory could also assist dermatologists by appending an interpretative comment to the lipid profile of children found to be at risk (LDL cholesterol ≥ 3.5 mmol/L) highlighting those individuals at potential risk for FH, which has previously been shown to significantly improve the detection rates.¹¹ However, it is likely that an FH awareness and education campaign is required for dermatologists to optimise detection, as significant gaps in FH knowledge have previously been uncovered in primary care, specialists and allied health professionals.²

The diagnosis and management of FH will need to be conducted within relevant regional guidelines.^{1,5,6} A diagnostic approach modified from the EAS child and adolescent

Table 1 Approach to identifying children with FH, modified from European Atherosclerosis Society child and adolescent guidelines⁶

LDL cholesterol	Action required
≥5.0 mmol/L	Repeat lipid profile with TSH, liver and kidney function tests and urine protein to exclude common secondary causes of elevated LDL-c. Refer to regional lipid service if repeat LDL-c ≥5.0 mmol/L.
4.0–4.9 mmol/L	Determine if a parent has a history of elevated LDL-c or premature CVD (males <55 years, females <60 years). Repeat lipid profile with TSH, liver and kidney function tests and urine protein to exclude common secondary causes of elevated LDL-c. Refer to regional lipid service if repeat LDL-c ≥4.0 mmol/L and a parent has elevated LDL-c or premature CVD.
3.5–3.9 mmol/L	Repeat lipid profile with TSH, liver and kidney function tests and urine protein to exclude common secondary causes of elevated LDL-c. Enquire if a parent has been diagnosed with FH. Refer to regional lipid service if repeat LDL-c ≥3.5 mmol/L and a parent has been diagnosed with FH.

CVD, cardiovascular disease; FH, familial hypercholesterolaemia; LDL-c, low density lipoprotein cholesterol; TSH, thyroid stimulating hormone.

guidelines⁶ is presented in Table 1. Approximately 10% of children would require additional questions regarding family history and/or repeat lipid testing, which should not overly burden a practising dermatologist.

In conclusion, dermatologists can play a significant role in the detection of FH by incorporating opportunistic screening for FH into their guidelines for managing isotretinoin therapy. However, further research is required to explore this potential method of opportunistic FH detection.

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Rapid detection of enteric pathogens in a medical assistance team by real-time multiplex PCR

Sir,

Diarrhoeal diseases acquired through contact with unhygienic conditions and contaminated food pose an ongoing risk to the health of travellers around the world.¹ A range of pathogens are known to cause diarrhoeal disease in travellers with *Escherichia coli* pathotypes and *Shigella* considered some of the most important.^{1–3} ‘Traveller’s diarrhoea’ is usually associated with travel from developed to underdeveloped areas of the world for a period of <2 weeks.¹ While the effects of diarrhoeal disease are typically mild (e.g., tolerable, no impact on activities), moderate (substantial symptoms; impacts on activity) to severe (dysentery; incapacitating) symptoms may develop.¹ Military and non-military personnel deployed to underdeveloped regions from developed countries face similar problems to the average traveller² with the cumulative time lost having the potential to significantly impact operations.⁴ In deployed settings, accurate and rapid surveillance and early treatment are thus essential to minimise loss of duty days.⁵

In December 2019, an Australian medical assistance team (AUSMAT) was internationally deployed to a South Pacific island nation, to assist local health services in managing an ongoing outbreak of viral illness amongst the population. The 32 person team consisted of civilian doctors, nurses, paramedics and logistics specialists with expertise in a range of skills including infectious diseases and microbiology. Mission diagnostic equipment included a BioFire FilmArray