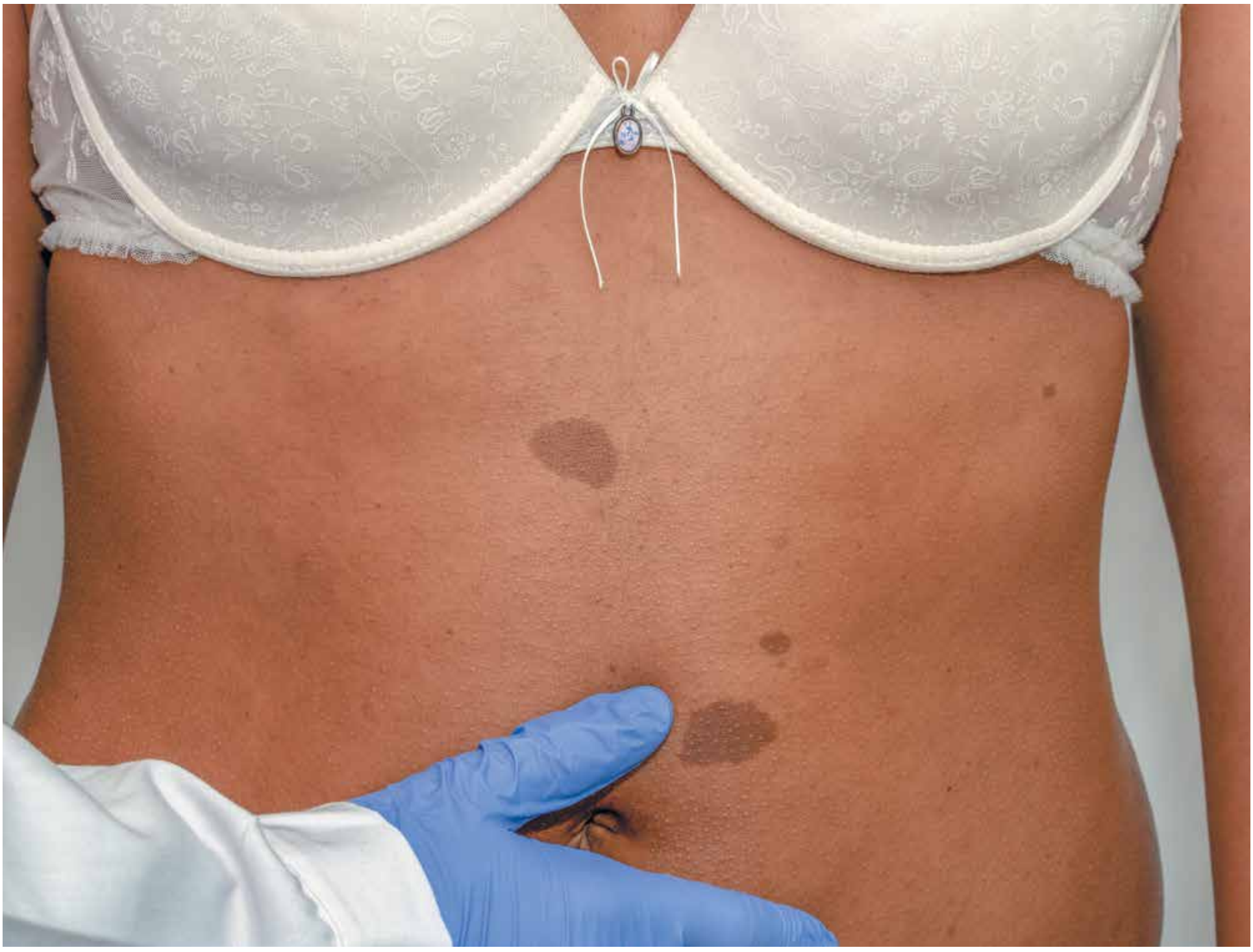


Neurofibromatosis type 1

Dr Megan Higgins
advanced trainee in clinical genetics at Genetic Health Queensland.

Professor Julie McGaughran
clinical geneticist, director at Genetic Health Queensland, [Claire: a title here?] Royal Brisbane & Women's Hospital, Qld.

Dr Helen Mar Fan
cancer geneticist at Genetic Health Queensland.

INTRODUCTION

NEUROFIBROMATOSIS type 1 (NF1), an autosomal dominant condition with a predisposition to benign and malignant tumours, is caused by pathogenic variants in the NF1 gene. The condition affects around 1/2500 worldwide.[1] NF1 may be inherited from a parent but approximately 50% of cases arise de novo.[2]

Signs generally appear in the first few years of life and the condition can vary in severity, even within families. Common features include cafe au lait macules, neurofibromas, Lisch nodules (iris hamartomas), freckling in the groin or axilla, and learning problems. Serious complications can include malignant peripheral nerve sheath tumours, optic pathway glioma, phaeochromocytoma, renal artery stenosis and cerebral gliomas.

Life expectancy for people with NF1 is reduced by 8-15 years because of cancer and cardiovascular complications.[3]

AETIOLOGY

NEUROFIBROMATOSIS type 1 is caused by mutations in the tumour suppressor gene NF1. The NF1 gene encodes neurofibromin, which is expressed in neurons and glial tissue in the central and peripheral nervous system.[4,5] Neurofibromin is a GTPase activating protein that downregulates the RAS signal transduction pathway, thereby controlling cellular proliferation.[2] Mutations in the NF1 gene cause unregulated RAS signalling, which contributes to tumour development.

CLINICAL FEATURES AND DIAGNOSIS

A CLINICAL diagnosis of NF1 can be made in the presence of two or more of the criteria (see box 1). The most common features are cafe au lait macules (present in more than 95% of infants) and skin fold freckling (in more than 80% of children by age seven).[2] Lisch nodules and cutaneous neurofibromas are found in more than 90% of adults with NF1. The diagnostic criteria are highly specific and sensitive in adults with NF1.[6]

An exception to the diagnostic criteria occurs in families where spinal NF1 is the predominant phenotype. These families have a high burden of spinal lesions but may not meet the diagnostic criteria for NF1.[8] Molecular testing is warranted in individuals with suspicious features of spinal NF1 where spinal lesions may not be distinguishable from related conditions (such as schwannomatosis) on imaging. Offer predictive testing for asymptomatic at-risk individuals to confirm or exclude the diagnosis.[8]

The diagnostic criteria for NF1 are currently under review and ▸

INSIDE

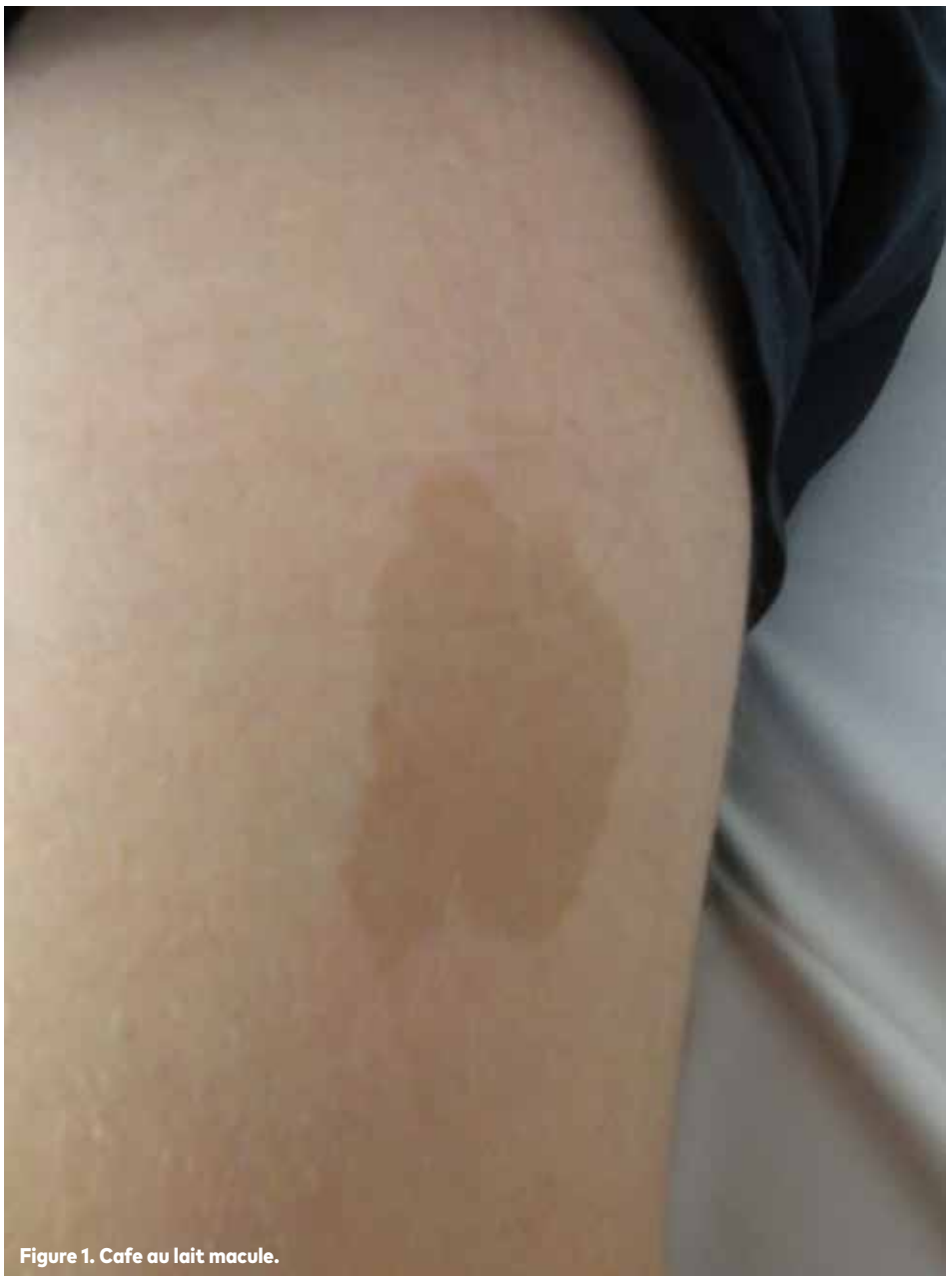


Figure 1. Cafe au lait macule.

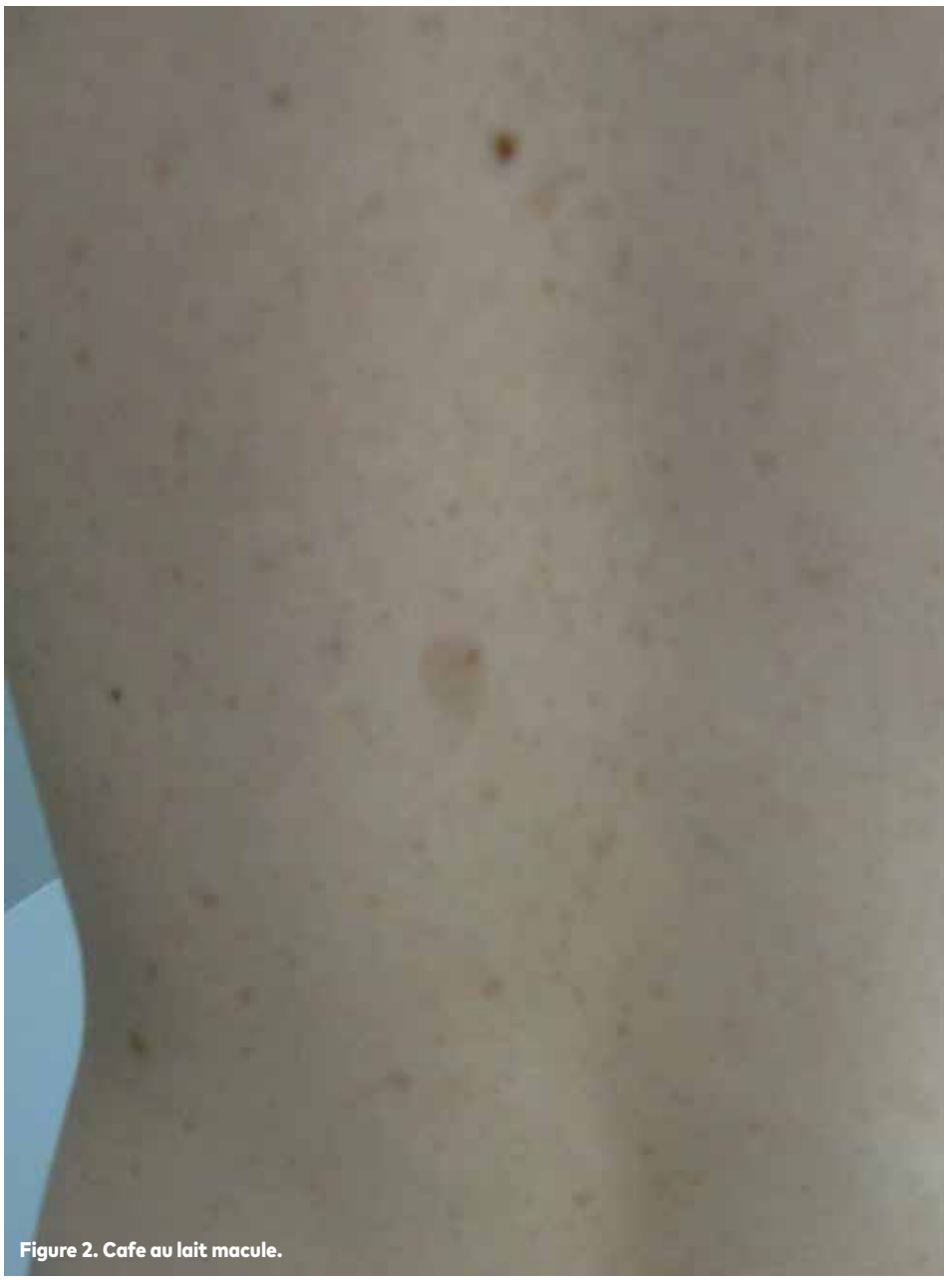


Figure 2. Cafe au lait macule.

◂ new guidelines are expected to be released later in 2019. In addition to the features listed in box 1, NF1 is associated with several other manifestations (see table 1).

Cutaneous manifestations

CAFE AU LAIT MACULES

A cafe au lait macule (see figures 1 and 2) is a hyperpigmented macule with a smooth, well demarcated border, which does not tend to cause complications.[1] They are typically present at birth and can increase in number in childhood.

SKIN FOLD FRECKLING

Skin fold freckling (see figure 3) can be found in the axilla, groin, at the base of the neck, under the breasts and on the upper eye lids.[1]

Neurofibromas

Neurofibromas are peripheral nerve sheath tumours that may be cutaneous, subcutaneous, spinal nerve root or plexiform tumours.[1,6] They are composed of Schwann cells, perineurial cells, axons, mast cells, fibroblasts, endothelial cells and extracellular matrix.[6]

Cutaneous neurofibromas (see figure 4) are benign and usually develop in late adolescence. They tend to increase in size and number with age, and during pregnancy.[6]

Subcutaneous neurofibromas are firm discrete lesions, which are evident on palpation.[6] They may cause peripheral nerve symptoms and, rarely, can transform to a malignant lesion.[1]

A plexiform neurofibroma is a multinodular growth that forms along the plexus of a nerve or along fascicles of single large peripheral nerves.[9] These tumours occur in about 50% of people with NF1. Complications - such as disfigurement, erosion of adjacent bone or blood vessel, obstruction of the respiratory or gastrointestinal tract, or progression to a malignant peripheral nerve sheath tumour - can occur.[10,11]

Cafe au lait macules ... are typically present at birth and can increase in number in childhood.

Ophthalmic manifestations

Lisch nodules (see figure 6 and 7) are pigmented iris hamartomas that are diagnosed on slit-lamp examination but can often be seen on physical examination. They are usually bilateral and do not cause visual problems. Other eye manifestations found in NF1 patients include choroidal abnormalities, congenital glaucoma and ptosis.

Neurological manifestations

Learning problems occur in around 30-69% of children with NF1, with a mean IQ in the range of 88-94.[12,13] Attention-deficit/hyperactivity disorder, autism spectrum disorder and sleep disorder are also well-recognised features of NF1.[1] MRI T2 hyperintensities occurring in the brainstem, cerebellum, basal ganglia, hippocampi, thalami and cerebral hemispheres are common in children with NF1.[4] Their presence has been linked to cognitive impairment however, there is no consistent conclusion as to whether this is causal.[6]

Around 4-13% of those with NF1 have seizures, with onset ranging from infancy to adulthood.[6] All seizure types are found in NF1 and they are usually mild compared with other neurocutaneous disorders. Status epileptics is rare.[6]

Skeletal manifestations

Bony abnormalities in NF1 include sphenoid wing dysplasia, long bone dysplasia (predominately the tibia) and scoliosis. Tibial PAGE 18 ▸

Box 1. Diagnostic criteria for neurofibromatosis type 1 (NIH consensus development conference 1988)

- Six or more café au lait macules (larger than 0.5cm in children or larger than 1.5cm in adults)
- Two or more cutaneous/subcutaneous neurofibromas or one plexiform neurofibroma
- Axillary or groin freckling
- Optic pathway glioma
- Two or more Lisch nodules
- Bony dysplasia (sphenoid wing dysplasia, bowing of long bone ± pseudarthrosis)
- First-degree relative with NF1

Source: Archives of Neurology 1998[7]

Table 1. Clinical manifestations

Clinical manifestation	Frequency (%)	Age of onset
Café au lait macules (CALMs)	More than 99	Birth to 12
Skin-fold freckling	85	Three to adolescence
Lisch nodules	90–95	Older than three
Choroidal abnormalities	More than 99	Older than two
Cutaneous neurofibromas	More than 99	Older than seven (usually late adolescence)
Plexiform neurofibromas	30 (visible) to 50 (on imaging)	Birth to 18
Disfiguring facial plexiform neurofibromas	3–5	Birth to five
Malignant peripheral nerve sheath tumour	2–5 (8–13% lifetime risk)	5–75
Scoliosis	10	Birth to 18
Scoliosis requiring surgery	5	Birth to 18
Short stature	30	Birth
Pseudarthrosis of tibia	2	Birth to three
Renal artery stenosis	2	Lifelong
Phaeochromocytoma	2	Older than 10
Severe cognitive impairment (IQ <70)	4–8	Birth
Learning problems	30-60	Birth
Macrocephaly	45	Birth
Epilepsy	67	Lifelong
Optic pathway glioma	15 (only 5% symptomatic)	Birth to 7 (up to 30)
Cerebral gliomas	2–3	Lifelong
Sphenoid wing dysplasia	1	Congenital
Aqueduct stenosis	1.5	Lifelong

Source: adapted from Ferner et al. 2007[1]*, Ferner and Guttman 2013*[6]

◂PAGE 16 dysplasia presents in early infancy with bowing with subsequent fracture, impaired healing and non-union (pseudarthrosis - see Figure 5).[14] Sphenoid wing dysplasia can lead to herniation of the temporal lobe into the orbit resulting in pulsating exophthalmos.[1] Scoliosis typically affects the lower cervical and upper thoracic spine, and severe scoliosis can lead to cord compression and respiratory compromise.[1]

Cancers

OPTIC PATHWAY GLIOMAS

Optic pathway gliomas are seen in around 15-20% of individuals with NF1. Children under seven years are at the greatest risk but the condition can occur at any age.[15] Optic pathway gliomas are usually pilocytic astrocytomas that have an indolent course, but approximately one-third to one-half of tumours cause symptoms.[1,15] Since young children rarely complain of visual loss, annual ophthalmic assessment is recommended (see Cancer Risk Management section). Optic pathway gliomas do not require treatment unless they are progressive or significantly reduce visual acuity.[1] Treatment involves surgery and/or chemotherapy to remove large orbital, hypothalamic or optic chiasm tumours.[1] Radiotherapy is not recommended for individuals with NF1 because of the high risk of secondary tumours.[15]

Women with NF1 are at moderately increased risk for breast cancer over their lifetime.

MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS

Malignant peripheral nerve sheath tumours are a type of soft-tissue sarcoma, which frequently arise from a pre-existing plexiform neurofibroma.[3,10] People with NF1 have about a 10% lifetime risk of developing a malignant peripheral nerve sheath tumour and the mean age of diagnosis is around 33.[3] The majority are high-grade tumours with a high rate of distant metastases and an overall five-year survival rate of around 34-52%.[9] Suspicion for this condition should be raised by the presence of rapid growth, pain, neurological symptoms, and early detection is essential for improved long-term survival.[3]

Risk factors for developing malignant peripheral nerve sheath tumours include personal or family history of the condition or other malignancy, a large number of subcutaneous neurofibromas or plexiform neurofibromas, neurofibroma neuropathy, germline microdeletion of the NF1 gene and previous treatment with radiotherapy.[3,6,10,11] The utility of routine screening with whole-body MRI is currently unknown.[3]

BREAST CANCER

Women with NF1 are at moderately increased risk for breast cancer over their lifetime. Breast cancer develops at a younger age compared with the general population, and there is a significantly poorer five-year survival and excess mortality.[3,16,17] The highest risk for breast cancer occurs between ages 30-39 (RR=6.5), then from 40 to 49 (RR=4.4), decreasing to the general population risk by age 70.[17]

PHAEOCHROMOCYTOMA

Phaeochromocytoma affects up to 2% of people with NF1 and around 12% are malignant.[1,18] The median age at diagnosis is 43, and 20% of cases are multifocal.[18] Suspect the diagnosis in a hypertensive individual with NF1, particularly if they are over 30 and have hypertension associated with palpitations, headache or sweating.[3]

OTHER MALIGNANCIES

Individuals with NF1 are also at risk of a number of other tumours, including brain and spinal cord glioma, tumours involving other endocrine glands, gastrointestinal stromal tumours, malignant fibrous histiocytoma and rhabdomyosarcoma.[3]

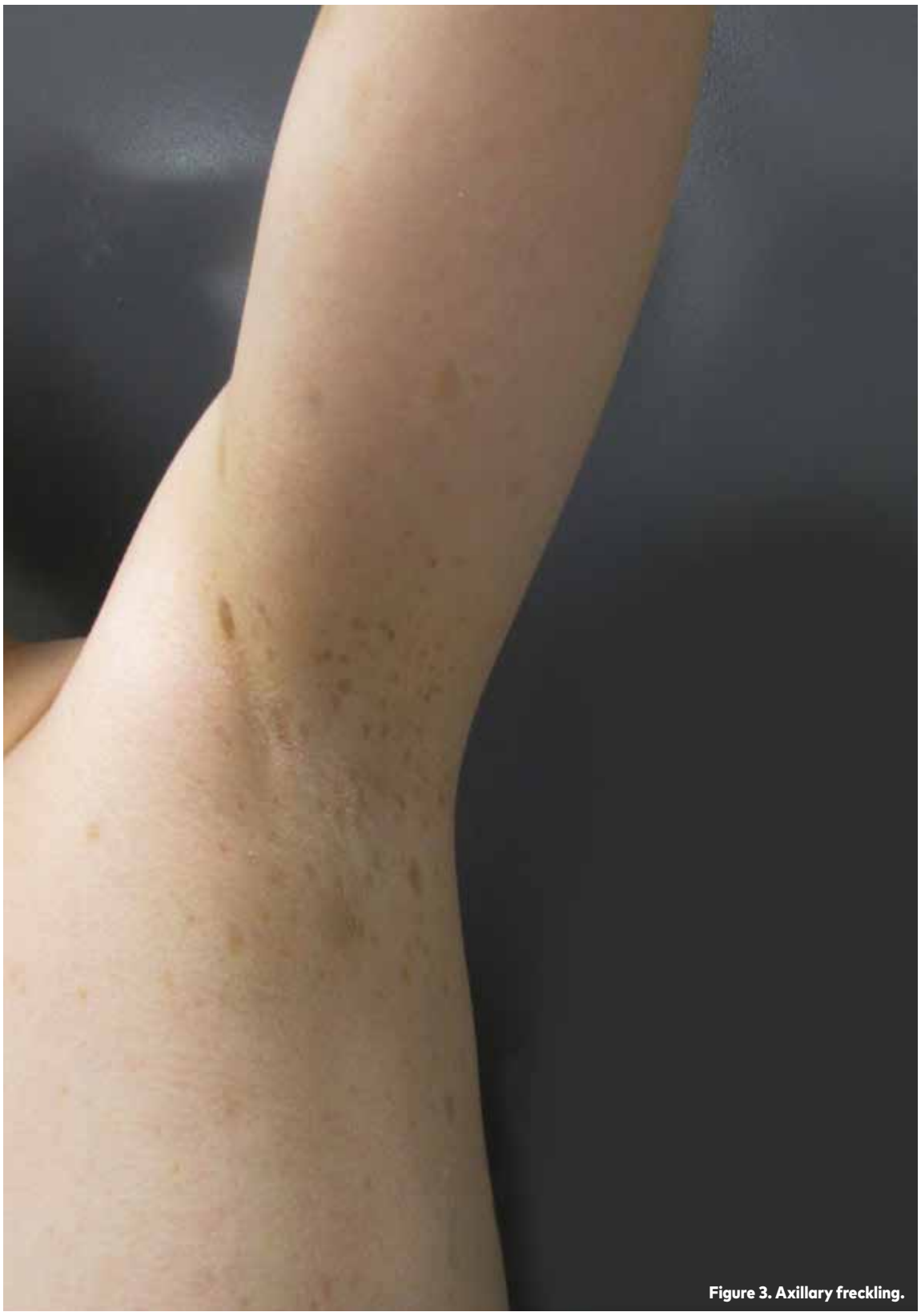


Figure 3. Axillary freckling.

Table 2. Differential diagnosis of NF1

Condition	Features shared with or similar to NF1	Features distinct from NF1
Legius syndrome (SPRED1 gene mutations)	Cafe au lait macules, skinfold freckling, learning difficulties, macrocephaly	Absence of CNS tumours, Lisch nodules, neurofibromas
Constitutional mismatch repair syndrome	Cafe au lait macules, axillary freckling	Young onset of Lynch syndrome cancers and family history of Lynch syndrome cancers
McCune-Albright syndrome / fibrous dysplasia (see figure 8)	Hyperpigmented macules	Hyperpigmented macules with irregular margins and polyostotic fibrous dysplasia
Noonan syndrome with multiple lentigines	Hyperpigmented macules	Multiple lentigines, ocular hypertelorism, hearing loss and congenital heart disease
Noonan syndrome	Some NF1 patients have a phenotype similar to Noonan syndrome	Short stature, webbed neck, congenital heart disease, characteristic facies
Neurofibromatosis type 2	Peripheral nerve tumours may resemble neurofibromas on imaging	Bilateral vestibular schwannomas, schwannomas in cranial and peripheral nerves, meningiomas, retinal hamartomas, juvenile cataracts
Schwannomatosis	Peripheral nerve tumours may resemble neurofibromas on imaging	Multiple peripheral nerve schwannomas, often with chronic pain
Segmental overgrowth syndromes (eg, Proteus syndrome, PIK3CA-related overgrowth)	Large neurofibromas or disfiguring facial plexiform neurofibromas may give the appearance of hamartomatous overgrowth or hemihypertrophy	Hemihypertrophy/asymmetry, hamartomatous overgrowth, epidermal naevi, haemangiomas
Piebaldism	Occasionally cafe au lait macules	Congenital hypopigemented patches of hair and skin

Box 2. Annual review in children

- Development, behaviour and progress at school
- Ophthalmological assessment for optic pathway gliomas and glaucoma (see Cancer Risk Management guidelines section)
- Head circumference (rapid increase might indicate tumour or hydrocephalus)
- Height (abnormal pubertal development)
- Weight (abnormal pubertal development)
- Pubertal development (delayed or precocious puberty due to pituitary or hypothalamic lesion)
- Blood pressure (renal artery stenosis, phaeochromocytoma)
- Cardiovascular examination (congenital heart disease, especially pulmonary stenosis)
- Evaluation of spine (scoliosis +/- underlying plexiform neurofibromas)
- Evaluation of the skin (cutaneous, subcutaneous and plexiform neurofibromas)
- System examination if specific symptoms

Source: Adapted from Ferner et al. 2007[1]

Box 3. Cancer risk management guidelines

- Optic pathway glioma
  - From infancy - six-monthly examination by an ophthalmologist
  - 4 to 16 years - annual examination by an ophthalmologist
  - From 16 years - 3 to 5 yearly ophthalmology assessment if no tumour has arisen in childhood
- Breast cancer
  - All ages - breast awareness and to seek review with general practitioner if concerns
  - From 35 to 40 years - annual MRI +/- ultrasound (US)
  - From 40 to 50 years - annual MRI +/- mammogram (MMG) +/- US
  - From 50 years - annual MMG +/- US
  - Pregnant - no MRI or MMG, consider US
- Phaeochromocytoma
  - Annual BP measurement
  - Consider fasting free plasma metanephrines if unexplained elevated BP
- Malignant peripheral nerve sheath tumours - from age 10 years
  - Annual clinical review with physical examination
  - Encourage early reporting of symptoms
  - Consider referral to a specialised sarcoma centre

DIFFERENTIAL DIAGNOSIS

THE differential diagnoses of NF1 are listed in table 2.

Genetic counselling and prenatal diagnosis

Approximately 50% of individuals with NF1 have de novo mutations and the remainder have inherited the condition from an affected parent.[2] The condition is inherited in an autosomal dominant fashion, meaning that children of individuals with NF1 have a 50% (1 in 2) chance of inheriting the condition. A small proportion of individuals have mosaic NF1, which may be milder or segmental, depending on the timing of mutation during embryogenesis.[6]

If the diagnosis of NF1 is suspected, refer the patient to a clinical genetics service for diagnostic clarification, management advice and genetic counselling. No additional imaging is generally required for making the diagnosis.

EviQ guidelines recommend that children under 16 are referred to an ophthalmologist for evaluation of optic pathway glioma.[19]

Prenatal diagnosis and preimplantation genetic diagnosis are available to adults with NF1 but first require a confirmed molecular diagnosis in the affected individual. If a patient is considering prenatal diagnosis or preimplantation genetic diagnosis, refer to a clinical genetics service, ideally prior to pregnancy.

Genetic testing for NF1 is available but many individuals do not require a genetic test to make the diagnosis. Situations where genetic testing can be of benefit include first, where a diagnosis of NF1 is suspected but the diagnostic criteria are not met, for example, in a child with more than six cafe au lait macules but no other features; second, in an adult (male or female) where prenatal or preimplantation genetic diagnosis is anticipated; and finally, in families with spinal NF1, molecular testing is indicated for at-risk relatives who may not meet the diagnostic criteria, especially in childhood.[8]

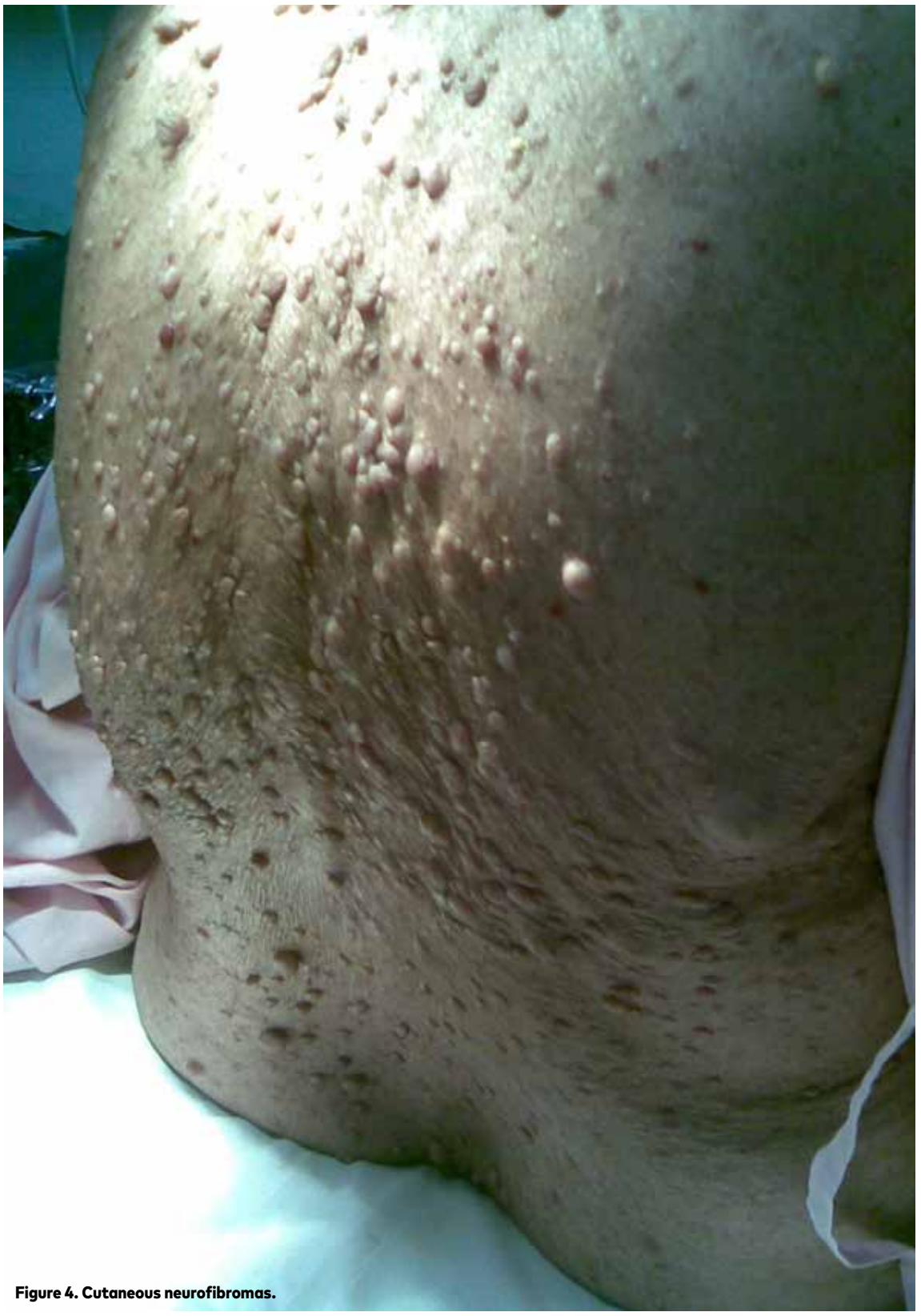


Figure 4. Cutaneous neurofibromas.

MANAGEMENT

THE MANAGEMENT of NF1 involves age-specific monitoring for disease manifestations. Encourage all individuals to report any unusual symptoms as serious complications may arise between reviews. A printable management checklist can be found on the EviQ website (see Online resources).[19]

Children with NF1

All children with uncomplicated disease need an annual assessment (see box 2), ideally by a general paediatrician.

Adults with NF1

Adults (16 years and older) with NF1 with uncomplicated features can be managed by their GPs with referral to specialist services where required. Refer complex cases - such as individuals with disfiguring neurofibromas, deforming skeletal lesions, spinal neurofibromatosis or history of malignancy - to an NF1 clinic or multidisciplinary team with experience in managing the condition.

As children transition into adulthood, referral to a genetics service is recommended, as they require genetic counselling and education about the condition and its possible complications. Offer psychological support, particularly as neurofibromas start to develop in late adolescence.

Annual blood pressure measurements are recommended for adults to screen for renal artery stenosis and phaeochromocytoma. Referral to an endocrinologist is indicated if phaeochromocytoma is suspected.

Encourage adults to check their skin for symptomatic lesions. Cutaneous neurofibromas are generally benign but may catch on clothes or become itchy. These lesions can cause significant psychological distress because of cosmetic problems. Referral to a surgeon skilled in removal of neurofibroma is recommended if any of these problems occur. Some centres offer dedicated dermatological clinics for management of cosmetic problems associated with NF1.

Plexiform neurofibromas may not be visible or palpable. Neurofibromas have a risk of transformation to malignant peripheral nerve sheath tumours. Thus, urgently refer any patient with persistent pain, new or unexplained neurological deficit, rapid increase in size of neurofibroma or change of texture to a specialist clinic or surgeon.

EviQ guidelines recommend that women with NF1 be referred for annual breast screening at age 35.[19]

The management of NF1 involves age-specific monitoring for disease manifestations.

Pregnant women with NF1

Neurofibromas may grow in size and number during pregnancy, and there is a risk of cord compression by expansion of a spinal plexiform neurofibroma.[1,6] Other considerations include pelvic neurofibromas impeding delivery, monitoring for hypertension, and attention to antiepileptic medication because of potential teratogenic effects.

Urgent referral to a clinical genetics service is indicated if there is a wish for prenatal diagnosis.

Urgent considerations

The following features should prompt urgent referral to the appropriate specialist:

- Skin: enlarging, hardening, painful or changing lumps.
- Eyes: evidence of squint, proptosis or reduced visual acuity.
- Neurological: onset of neurological symptoms, such as ataxia, visual disturbance, leg/arm weakness or paraesthesia, headaches, loss of consciousness.
- Increasing pain in any region of the body where the cause of pain cannot be easily discerned from clinical examination.
- Breast lumps.

Cancer risk management guidelines

The Australian guidelines for cancer risk management in individuals with NF1 are listed in box 3 (available from the EviQ website).[19]

CASE STUDIES

Case study one

SOPHIA, 18, is referred by her neurologist to the genetics service for counselling and testing for NF1. She was clinically diagnosed with NF1 at 14 after undergoing an MRI knee for recurrent patella dislocations after a fall. The MRI demonstrated a plexiform neurofibroma affecting the common peroneal nerve.

She has a history of learning difficulties at school and recurrent headaches. There is no history of hypertension, which was routinely monitored by her GP. When Sophia was 17, her mother requested a referral to a neurologist as she felt more screening was required. The neurologist arranged an MRI of the brain and spine, which showed a hypointense lesion around the cerebral aqueduct causing obstructive hydrocephalus. Sophia subsequently underwent insertion of a ventriculoperitoneal shunt. Ophthalmological and neuropsychologist assessments were also arranged.

On review in the genetics clinic, the diagnosis of NF1 is confirmed. Sophia has seven cafe au lait macules measuring more than 15mm, axillary and groin freckling, and three small subcutaneous lumps likely to be subcutaneous neurofibromas. Head circumference measures above the 99th centile.

Her mother, who attends the appointment with her, is examined for signs of NF1, which are absent.

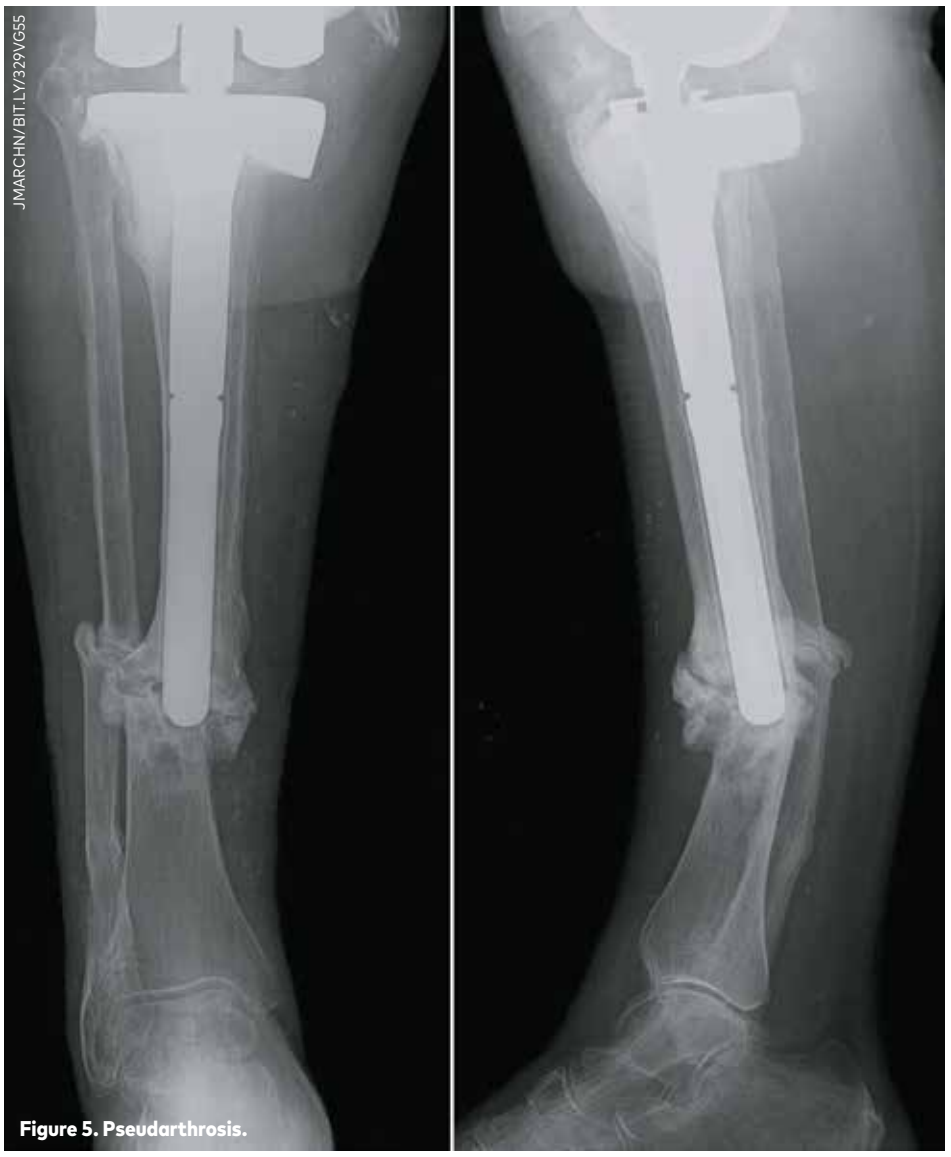
Sophia and her mother are re-educated on the clinical features, inheritance and management of NF1, including when to seek urgent medical attention. For adults with NF1, annual blood pressure monitoring (for hypertension secondary to renal artery stenosis or phaeochromocytoma) is recommended. Women with NF1 are at a moderately increased risk of breast cancer over their lifetime, with the highest risk between ages 30 and 49. Though breast screening is not currently relevant to the patient, it is important for her to be aware of the risk management guidelines to ensure she is referred to breast screening at the appropriate age. Reproductive planning options are discussed, such as preimplantation genetic diagnosis and prenatal diagnosis. Sophia is not currently planning children, however, genetic testing for the NF1 gene is offered so that a molecular diagnosis can be confirmed prior to family planning.

Case study two

ANDREW, 10, presents with a one-week of headaches, vomiting, unsteady gait and visual changes. He has a history of developmental delay and mild learning difficulties requiring support at school. There is a left-sided facial mass that has been present for four years. There is no significant family history.

Physical examination reveals macrocephaly, multiple cafe au lait macules larger than 5mm, and axillary and groin freckling. There is a soft, non-tender mass with an irregular border in the region of the left parotid gland.

MRI brain and spine reveal a mass within the left cerebral peduncle obstructing the cerebral aqueduct, causing hydrocephalus, an optic pathway glioma, a lesion protruding into the left lateral ventricle and background changes consistent with NF1. Ultrasound of the left cheek shows a parotid lesion with an irregular outer margin with multiple hypoechoic foci within the gland.



JMARCHN/BIT.LY/329VG55

Figure 5. Pseudarthrosis.

Figure 6. Lisch nodules.

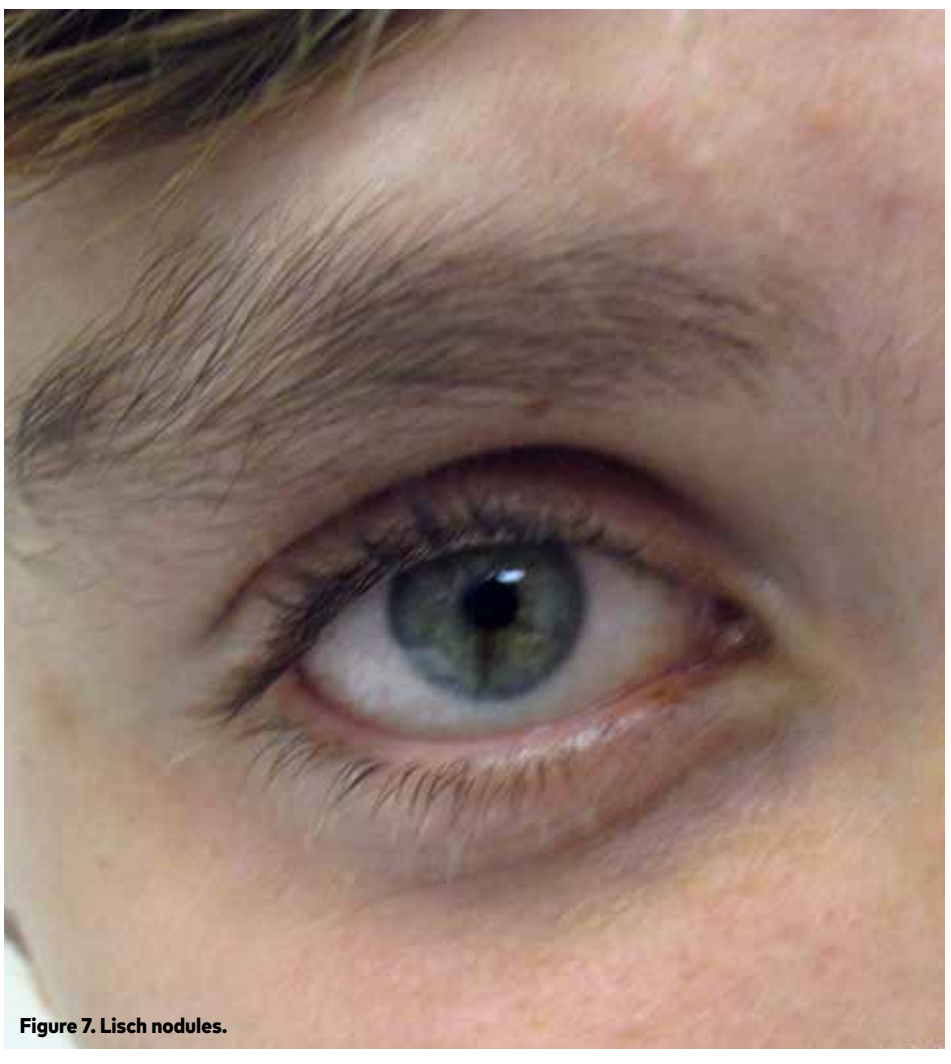
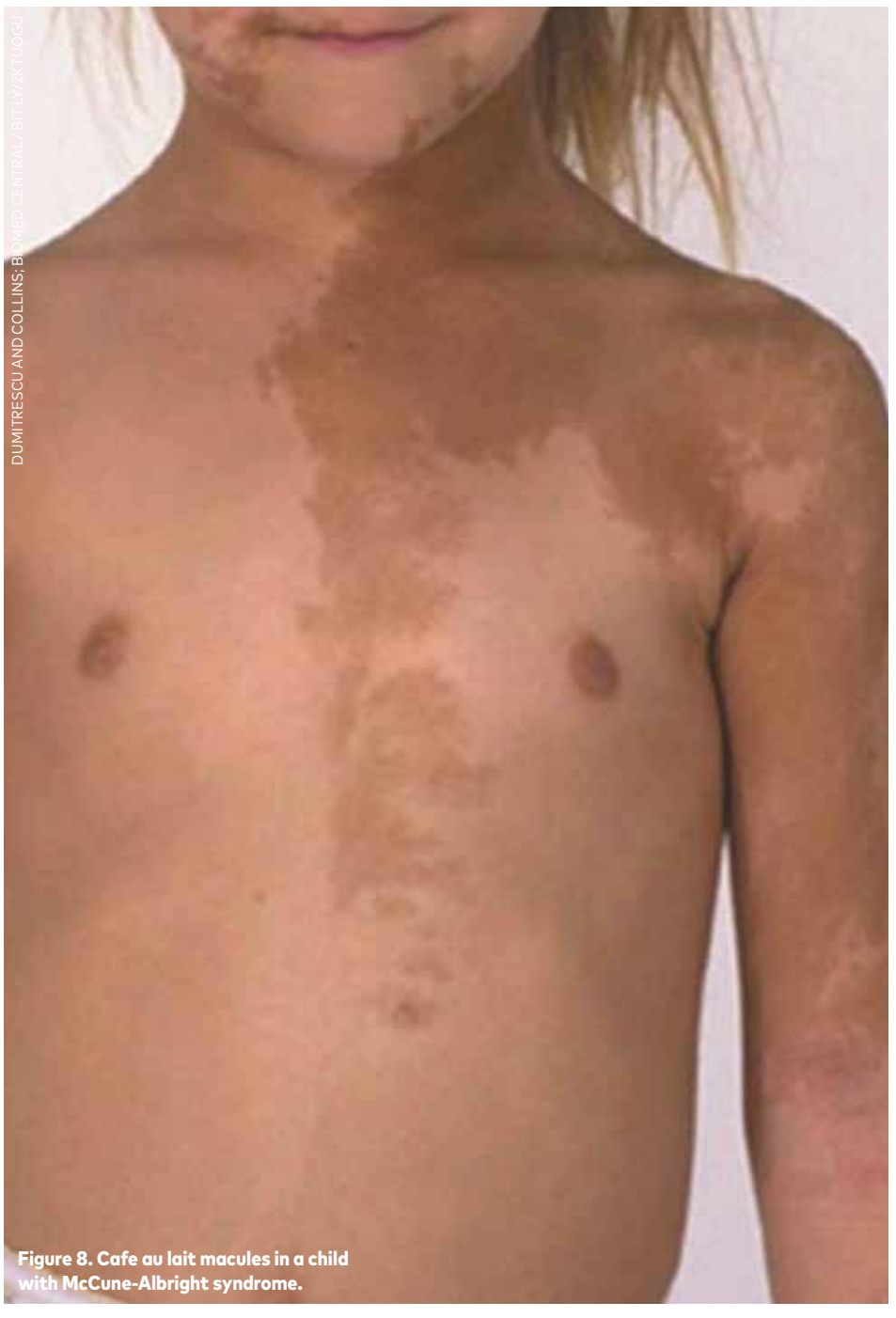


Figure 7. Lisch nodules.



DUMITRESCU AND COLLINS; BIOMED CENTRAL / BIT.LY/2KTUOGU

Figure 8. Cafe au lait macules in a child with McCune-Albright syndrome.

Andrew starts dexamethasone and undergoes emergency shunt insertion, followed by debulking of the cerebral peduncle lesion a few weeks later. Histopathology on the tumour shows a pilocytic astrocytoma, WHO grade 1. Chemotherapy is not initiated and the brain lesions monitored on a three-monthly basis for signs of progression. A biopsy of the parotid gland lesion shows a plexiform neurofibroma. Ophthalmology review confirms the presence of Lisch nodules.

Based on the clinical findings, a diagnosis of NF1 is made. His mother's examination findings are unremarkable. His father and siblings are not present at the time of review. The diagnosis of NF1 is discussed, including the clinical features, inheritance pattern and management considerations. Other family members are referred to a genetics service for assessment of NF1. Andrew is advised to attend a genetics service in his late teens/young adulthood for genetic counselling, management advice and possible genetic testing for future reproductive planning. He has ongoing follow-up with oncology, ophthalmology, neurosurgery and paediatrics.

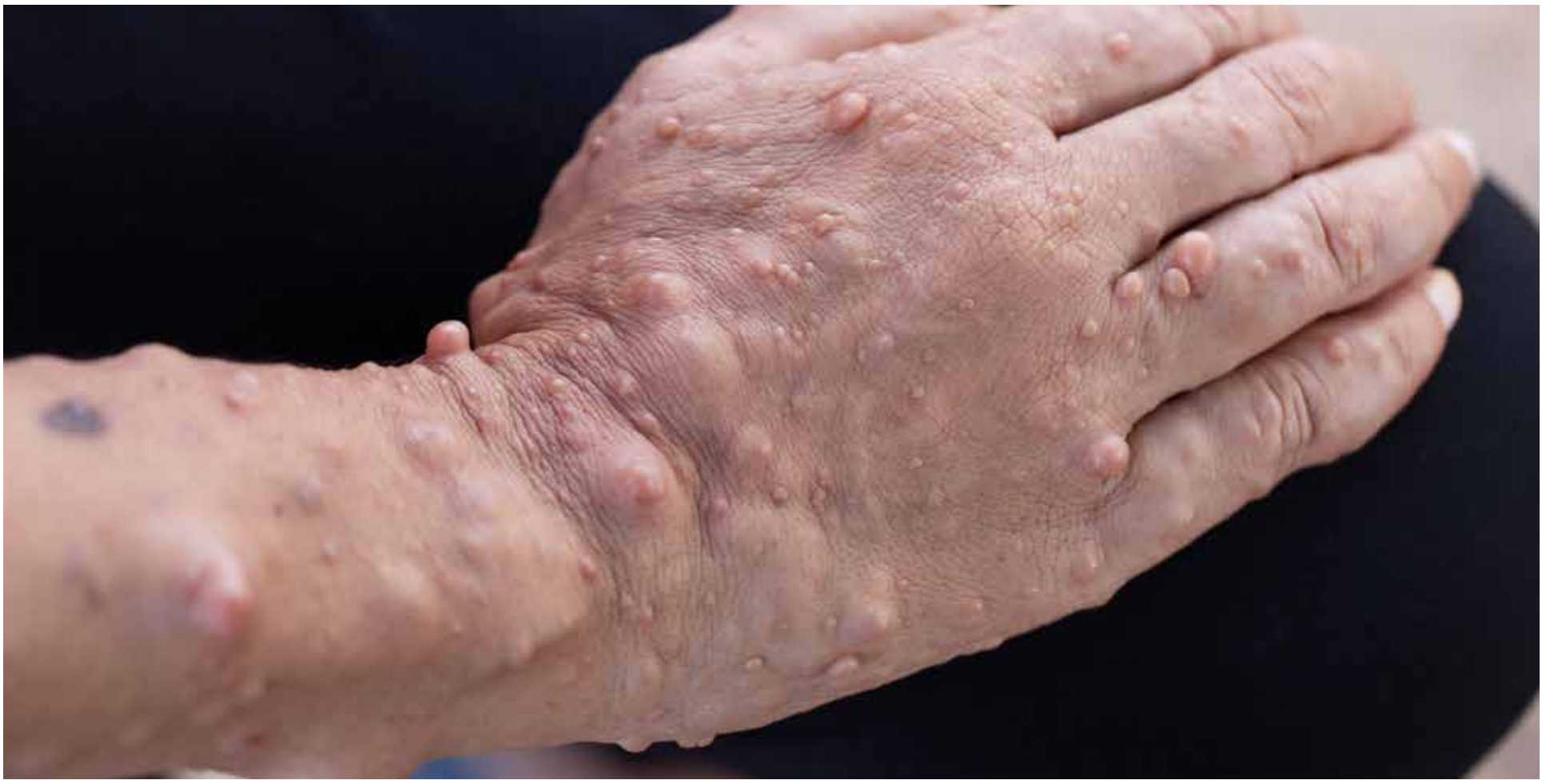
Jim was diagnosed with NF1 in childhood ... his main concern is the disfigurement caused by neurofibromas.

Case study three

JIM, 37, is referred by his GP for diagnostic clarification of NF1. He has multiple cutaneous neurofibromas increasing in number over time. Several of the lesions are confirmed to be neurofibromas on histopathology. He was diagnosed with NF1 in childhood but no further follow-up or screening was initiated. His main concern is the disfigurement caused by neurofibromas.

He had learning problems at school. There is no family history of NF1 and he is not aware of other family members with cafe au lait macules or neurofibromas. Jim does not have children and is not planning to have any.

PAGE 22 ▶



◂PAGE 20 Examination reveals macrocephaly, multiple cutaneous and subcutaneous neurofibromas, axillary and groin freckling and five cafe au lait macules measuring more than 15mm. Lisch nodules are present. A clinical diagnosis of NF1 is confirmed. Genetic testing is not initiated as Jim is not planning to have children. The diagnosis of NF1 is discussed, including clinical features, management recommendations and genetic counselling.

Specific management recommendations include annual blood pressure measurement and surveillance for rapidly changing or painful neurofibromas, neurological changes or unexplained pain. Family members can be referred by their GPs for assessment of NF1.

Jim's GP is advised to refer him to a dermatology clinic specialising in treatment of neurofibromas.

CONCLUSION

NF1 is an autosomal dominant condition with a predisposition to developing benign and malignant tumours, as well as several non-cancer-related manifestations. Diagnosis can be made on clinical criteria, but genetic testing is available. Age-related risk management guidelines are available.

ONLINE RESOURCES

- **Children's Tumour Foundation** www.ctf.org.au
- **Genetics services by state**
  Queensland (Genetic Health Queensland) bit.ly/2uR8ehm

  NSW bit.ly/2XJslNv

  Victoria, Tasmania and NT bit.ly/2W2ErAN

  SA (SA Clinical Genetics Service) bit.ly/2W3NpO0

  WA (Genetics Services of WA) bit.ly/2UAxtkK
- **EviQ review checklist Neurofibromatosis Type 1** bit.ly/2VjJyzr

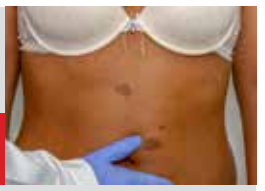
References
Available on request from howtotreat@adg.com.au

Key points

- NF1 is an autosomal dominant condition affecting around 1/2500 individuals.
- Diagnosis can be made clinically based on well-established diagnostic criteria.
- Many patients with NF1 can be managed by their GPs. Refer complex patients to a specialist NF1 clinic or a specialist experienced in NF1 associated health problems.
- Urgent assessment is required for rapidly growing lesions, unexplained pain, breast lumps, new onset of neurological symptoms or visual changes.

How to Treat Quiz.

NEUROFIBROMATOSIS TYPE 1



GO ONLINE TO COMPLETE THE QUIZ **www.ausdoc.com.au/howtotreat**

1. **Which TWO statements regarding neurofibromatosis type 1 are correct?**
   - **a** NF1 may be inherited from a parent but around 50% of cases arise de novo.
   - **b** Common features include cafe au lait macules, neurofibromas, Lisch nodules, freckling in the groin or axilla, and learning problems.
   - **c** Neurofibromatosis type 1 is an autosomal recessive condition with a predisposition to benign and malignant tumours.
   - **d** Life expectancy for people with NF1 is reduced by 15-20 years because of cancer and cardiovascular complications.

2. **Which THREE are part of the list of diagnostic features for neurofibromatosis 1?**
   - **a** Axillary or groin freckling.
   - **b** Family history of NF1.
   - **c** Two or more Lisch nodules.
   - **d** Six or more café au lait macules (greater than 0.5cm in children or greater than 1.5cm in adults).

3. **Which THREE features occur with a frequency of greater than 99% in neurofibromatosis 1?**
   - **a** Skin-fold freckling.
   - **b** Café au lait macules.
   - **c** Choroidal abnormalities.
   - **d** Cutaneous neurofibromas.

4. **Which TWO clinical features of neurofibromatosis 1 may be visible at birth?**
   - **a** Café au lait macules.
   - **b** Microcephaly.
   - **c** Lisch nodules.
   - **d** Scoliosis.

5. **Which TWO statements regarding the clinical features of neurofibromatosis 1 are correct?**
   - **a** Cutaneous neurofibromas are benign and usually present at birth.
   - **b** All seizure types are found in NF1 and they are usually mild compared with other neurocutaneous disorders.
   - **c** Lisch nodules should be excised on diagnosis, as their presence progressively impairs vision.
   - **d** Severe scoliosis can lead to cord compression and respiratory compromise.

6. **Which THREE statements regarding neurofibromatosis 1 and cancer are correct?**
   - **a** Children under seven are at the greatest risk of optic pathway gliomas.
   - **b** Breast cancer develops at a younger age compared with the general population and there is a significantly poorer five-year survival and excess mortality.
   - **c** The majority of malignant peripheral nerve sheath tumours are low-grade with an excellent overall five-year survival rate.
   - **d** Suspect phaeochromocytoma in patients with hypertension associated with palpitations, headache or sweating.

7. **Which TWO are differential diagnoses of neurofibromatosis 1?**
   - **a** Vitiligo.
   - **b** Tuberous sclerosis.
   - **c** Neurofibromatosis 2.
   - **d** Noonan syndrome.

8. **Which THREE are part of the annual review of a paediatric patient with neurofibromatosis 1?**
   - **a** Height, weight and head circumference.
   - **b** Biopsy of all new skin lesions.
   - **c** Ophthalmological assessment.
   - **d** Blood pressure.

9. **Which TWO are indications for urgent referral?**
   - **a** Increasing number of café au lait macules.
   - **b** Evidence of squint, proptosis or reduced visual acuity.
   - **c** Onset of neurological symptoms.
   - **d** Breast tenderness.

10. **Which THREE are risks for pregnant women with neurofibromatosis 1?**
    - **a** Hypotension.
    - **b** Cord compression by expansion of a spinal plexiform neurofibroma.
    - **c** Pelvic neurofibromas impeding delivery.
    - **d** Potential teratogenic effects from antiepileptic medication.

CPD POINTS

- We have a new How to Treat website (www.ausdoc.com.au/howtotreat) where you can read this article and take the quiz to earn CPD points.
- Each article has been allocated 2 RACGP QI&CPD points and 1 ACRRM point.
- RACGP points are uploaded every six weeks and ACCRM points quarterly.