Dear Practitioner,

Breast Cancer risk in NF1 females

Neurofibromatosis type 1 (NF1) is an autosomal dominant inherited tumour predisposition syndrome caused by pathogenic variants in the *NF1* gene.[1] The condition has a high *de novo* mutation rate with around 50-60% of affected individuals being the first in their family. Estimates of birth incidence and prevalence range from 1 in 2,000-2,700 and 1 in 4,000-4,500 respectively.[2,3] The condition can be diagnosed when at least two of eight major criteria are met. A major criterion and the feature that gives the condition its name is the presence of neurofibromas, on the skin or deep seated nodular or plexiform neurofibromas that can act as precursors to malignant peripheral nerve sheath tumours (MPNST) which are a major cause of early death.[4,5] Another universal feature is the presence of café au lait birthmarks which are present from birth or soon after

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For many years, evidence for an increased risk of common cancers in patients with NF1 was largely limited to case reports.[6–10] Several large studies have now confirmed an increased risk of breast cancer with a lifetime risk of about 20% but importantly a 5-fold risk under 50 with a risk to age 50 of 10% compared to 2% for the average women. This meets NICE criteria for moderate risk with a lifetime risk above 17% and a 10-year risk aged 40 of ~5% (4.2-14%) which is greater than the required 3% by NICE.

NF1 females should therefore in accordance with NICE guidelines be referred for annual mammography screening between 40-50 years of age.

A summary of the relative risks in six cohort studies is shown in Table 1. Taken together, these epidemiological studies reflect that at least half of the breast cancers diagnosed in women with NF1 were under 50 years of age, whereas in the general population, <20% occur by this age. [9,11] The highest incidence in NF1 is in women younger than 40 years of age, with mortality rates higher than those for women with breast cancer in the general population.[5,9,14] The cumulative risk for breast cancer by the age of 40 years is 4.7%, over 10 times that of the general population.[9] This absolute risk rises to around 10% by age 50 years in NF1. NF1 breast cancers on average are more aggressive with higher mortality rates. Screening in one centre in Italy showed improved survival.[9,12,13,14]

Please therefore refer any woman with NF1 to a local family history clinic for screening between 40-50 years of age.

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Table 1: Estimated SIRs from 6 cohort studies for breast cancer (BC) risk under age 50 years

Reference	Country	SIR <50 (95%CI)	10-year BC risk 30 years general population UK	Estimated 10-year BC risk 30 years NF1 UK	10-year BC risk aged 40 years general population UK	Estimated 10-year BC risk aged 40 years in NF1 UK
Walker et al[6]	UK	4.02 (1.09–10.3)	0.50%	2%	1.60%	6.50%
Sharif et al[7]	UK	4.9 (2.4- 8.8)	0.50%	2.50%	1.60%	7.80%
Wang et al[8]	USA	8.8 (3.2–19.2)	0.50%	4.40%	1.60%	14%
Madanikia et al[10]	USA	4.41 (1.12-12.00)	0.50%	2.20%	1.60%	7%
Seminog and Goldacre[11]	UK	30-39=6.5 (2.6–13.5), 40–49=4.4 (2.5–7.0),	0.50%	3.20%	1.60%	7%
Uusitalo et al[9]	Finland	<40=11.1 (5.6–19.5) 40–49=2.6 (0.95–5.65)	0.50%	5.50%	1.60%	4.20%

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