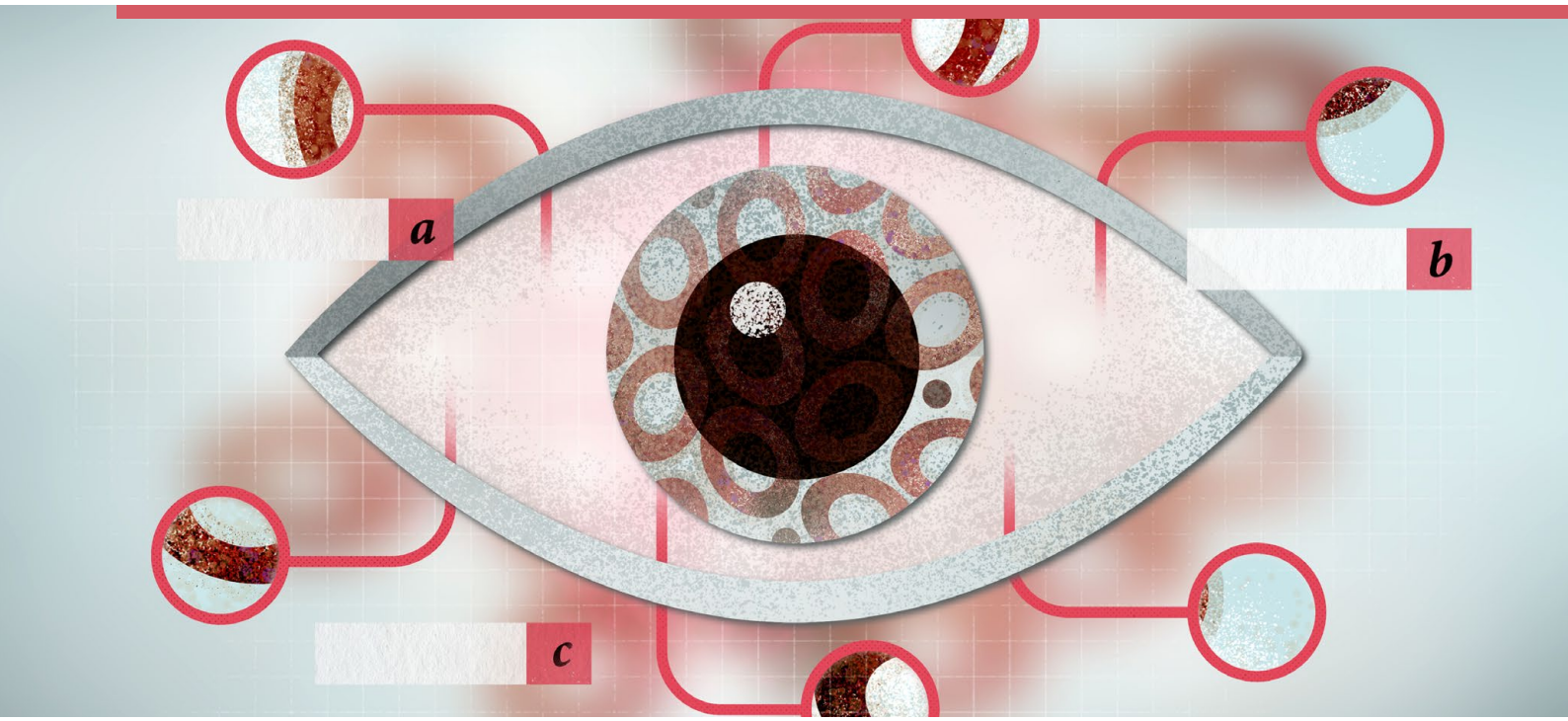

Melanoma: post-treatment follow-up and surveillance

Post-treatment follow-up and long-term surveillance of people with a history of melanoma improves the likelihood that recurrence (or a new primary melanoma) will be identified early. In most cases, melanoma recurrence is self-detected. However, ongoing primary care follow-up is still essential to provide a more comprehensive assessment for recurrence and surveillance of new lesions of concern, and to deliver ongoing education and support.

KEY PRACTICE POINTS:

- Multiple factors influence the risk of local recurrence or distant metastases; the risk is highest in the years immediately following treatment and reduces over time
- Melanoma recurrence is self-detected in up to 75% of cases; in addition to looking for suspicious skin lesions, patients should be aware of other features that may indicate recurrence, e.g. hardened lumps under the skin, enlarged lymph nodes or persistent and unexplained systemic symptoms
- Approximately 5 – 10% of patients develop a second invasive melanoma and more than 20% develop a new melanoma *in situ* at some point after their initial diagnosis
- Clinical follow-up is essential to provide a more comprehensive assessment for recurrence or the development of a new primary tumour, the detection of lymphoedema, to evaluate the clinical significance of any reported symptoms and to deliver ongoing education, reassurance and psychosocial support; this can occur in primary care for most patients, but secondary care follow-up may be required for some patients with advanced disease or other medically complex needs
- The frequency and duration of clinical follow-up is generally based on the patient's staging at diagnosis but may need to be individualised depending on the patient's needs, objectives or other circumstances, e.g. the presence of many melanocytic or atypical naevi
- Routine laboratory monitoring is not recommended for detecting recurrence in asymptomatic patients as abnormal blood findings are rarely the first sign of metastases and laboratory tests have a low level of specificity for melanoma recurrence
- Ultrasound assessment of draining nodal basins may be appropriate for some patients, in addition to clinical examination, e.g. patients with sentinel node biopsy-positive stage III melanoma where lymphadenectomy has not been performed
- Routine follow-up with cross-sectional imaging (e.g. CT and MRI) is generally only indicated for patients with stage II-C melanoma onwards, or when recurrence or metastatic disease is suspected based on clinical presentation, history or findings on ultrasound examination

For information on early detection of melanoma, see: "Early detection of melanoma and assessment of asymptomatic people at high risk", available from **bpac.org.nz/2021/melanoma-detection.aspx**

Follow-up is essential to identify melanoma recurrence as early as possible

Localised control of melanoma is of major clinical importance. For patients with early-stage cutaneous melanomas that were identified and excised promptly, surgery can be essentially "curative" in many cases.[1] However, melanoma has a significant metastatic capacity and can spread from relatively small primary sites to multiple locations throughout the body.[2] Given that the five-year survival rate for patients with metastatic melanoma is 15 – 25%,[3, 4] follow-up and surveillance are essential after the initial diagnosis and treatment of a primary tumour to identify recurrence at the first possible opportunity.

Estimates of melanoma recurrence rates vary substantially across the published literature according to the study population, patient staging at diagnosis and the treatment received.[5] Comprehensive data on melanoma recurrence in New Zealand is not available; a 2011 Australian study reported that recurrence occurred in 24% of patients diagnosed with stage I or II melanoma between 1985 and 2009.[6]

A number of mechanisms can be associated with recurrence, including:[7]

- **Local recurrence** – when regrowth occurs close to the original primary tumour, generally defined as being within 2 cm of the original scar. Local recurrence can occur either through incomplete surgical excision of the primary melanoma or malignant cells spreading within the local area from the tumour via the lymphatic system or blood vessels.
- **In-transit metastases** – melanoma deposits more than 2 cm from the primary tumour scar resulting from spread through the regional dermal and subdermal lymphatic system
- **Nodal metastases** – when metastases from the primary tumour reach the regional lymph nodes, usually causing enlargement
- **Haematogenous metastases/distant metastases** – when malignant cells enter the bloodstream, either secondary to lymph node involvement, or through direct invasion of local blood vessels around the primary tumour. Once metastases are in the bloodstream, they can disseminate throughout the body, deposit in organs/tissue and proliferate. Haematogenous metastases most commonly occur in or beneath the skin (anywhere on the body), the lungs, liver and brain.

A new primary melanoma may develop independently in patients with a history of melanoma and may be mistaken for local recurrence of the primary melanoma if it occurs close to the excision site.[7] The risk of developing a new primary melanoma varies between patients and risk factors can be different to those that led to the development of the original primary melanoma.[8] Approximately 5 – 10% of patients develop a second invasive melanoma and more than 20% develop a new melanoma in situ at some point after their initial diagnosis.[9]

Risk factors associated with melanoma recurrence

The risk of local melanoma recurrence or metastases varies substantially between patients and is most strongly correlated with their staging at diagnosis.[1] This includes factors such as tumour ulceration, thickness and sentinel lymph node positivity. One randomised controlled trial of 740 patients with lesions of the trunk and proximal extremities demonstrated a six-fold increase in local recurrence rates if the primary tumour was ulcerated.[10] Likewise, thicker primary melanomas at the time of resection are associated with an increased risk of recurrence; metastases are uncommon in people with tumours < 1 mm in depth (< 5%), whereas those with tumours > 4 mm in depth have an approximately 40% chance of metastases.[9]

Other risk factors. Despite the importance of staging in predicting recurrence, this approach does not encompass all possible risk factors. In New Zealand, most clinicians refer to the American Joint Committee on Cancer (AJCC) staging guidelines, and these have been progressively revised over time. In their current form (AJCC 8), the criteria do not incorporate mitotic rate – a measure of how rapidly cells in the tumour are proliferating – mostly because there is a strong positive correlation between this variable and tumour thickness.[11] A 2019 study of patients with high-risk primary tumours found that those with a mitotic rate > 3 mitoses/mm^2 were almost 2.5 times more likely to experience recurrence.[12] An estimation of mitotic rate is usually detailed on pathology reports. The presence of satellite lesions and resection margins < 1 cm also increase the risk of recurrence.[1, 13] In addition, recurrence is also more likely in males, however, the reason for this is unknown.[1]

There are no validated New Zealand-specific tools for calculating a patient's risk of melanoma recurrence or of developing a subsequent primary melanoma . For an example of an Australian tool, see: **www.melanomarisk.org.au**

N.B. People living in New Zealand should enter 'Tasmania' as the 'Region of Australia most lived in' to receive the most appropriate risk profile.

Time to recurrence is unpredictable – but it *generally* occurs "sooner rather than later"

It is not possible to accurately predict the time to recurrence for melanoma. Overall, the risk of melanoma recurrence reaches a peak approximately one year after the initial diagnosis; the

risk of recurrence occurring in local skin, distant skin and lymph nodes peaks after eight months, while the risk in the lungs and other distant sites peaks after 24 months.[14] At least 80% of recurrences are within the first three years following diagnosis.[15] However, melanoma recurrence can occur many years after an initial diagnosis regardless of the initial staging, e.g. > 10 years, and a new melanoma can develop at any time.[15] Therefore, while primary care follow-up is generally more frequent to begin with, it should continue less frequently but long-term for all patients with a history of melanoma (see: "A general guideline for the frequency of follow-up").

Most melanoma recurrences are self-detected

It is estimated that up to 75% of melanoma recurrences are first detected by the patient, rather than by a health practitioner.[15] As such, once a patient has been initially treated for a primary melanoma, it is essential to reinforce the importance of full monthly body self-checks, including lymph node examination. Emphasise the "ugly duckling" principle (i.e. looking for lesions dissimilar in appearance to others on the body) and the ABCDEFG checklist; alternatively, a simpler acronym such as SCAN (sore, changing, abnormal, new) may be easier for the patient to remember.[8, 9] Use of a mirror or assistance from another person may be needed to assess areas that are hard to see, e.g. the back or scalp.

For further information on self-checks for melanoma, including patient information for spotting an "ugly duckling" and the ABCDEFG checklist, see:

- **https://www.melanoma.org.nz/early-detection**
- **https://www.sunsmart.org.nz/**

If patients are interested in using smartphone teledermatology for self-checks, recommend that they only use a validated application. For options, see: **https://www.healthnavigator.org.nz/apps/s/skin-check-apps/**

Additional self-check considerations for identifying recurrence

Patients should already be familiar with sun smart principles and the process of self-checking their skin as these are important discussion points following the identification of their primary melanoma. However, patients should also be informed of symptoms and signs that may suggest potential recurrence, which include:[1]

- Any new lesions close to the surgical excision site, i.e. regardless of whether they are "ugly ducklings"; skin and subcutaneous metastases at other sites on the body which may vary in appearance, but are often round, firm and pigmented
- Hardened lumps under the skin; this can occur in isolation, but is particularly indicative of metastasis if multiple nodules develop within a localised area
- Enlarged or painful lymph nodes
- Other indicators of distant metastases, e.g. shortness of breath, persistent cough, haemoptysis, a persistent loss of appetite or abdominal pain, chronic headache or the onset of cognitive deficits, unexplained fatigue or unexplained gastrointestinal symptoms

Follow-up in primary care

After the initial treatment of a patient with melanoma, a lead clinician needs to be nominated to maintain and action patient follow-up. Assuming all hospital-level care has been completed, this often becomes the responsibility of the patient's general practitioner. Continued secondary care follow-up is usually only required for some patients with advanced melanoma or other medically complex needs.

The objectives of follow-up are to:[1, 8]

Detect any potential recurrence or new melanoma that may not have been identified by the patient during self-checks and to detect lymphoedema. The physical evaluation should include a review of the primary melanoma excision site, potential in-transit pathways towards the lymph nodes and palpation for lymph node enlargement. A full body skin examination, including the scalp, should be performed at least annually in primary care; any new or suspicious lesions should be examined using dermatoscopy.

Identify other features that may indicate distant metastases; particular attention should be given to any symptom(s) that have increased in intensity or frequency over time, or other unexplained systemic features

Deliver ongoing education, including reinforcing the importance of sun smart principles and skin self-checks

Assess the patient's mental health and emotional wellbeing (see: "Assess the patient's wellbeing at each appointment")

N.B. It is not intended that all aspects of follow-up are covered in the same appointment. These checks may take place in dedicated follow-up appointments, opportunistically during appointments for other reasons and over time.

A general guideline for the frequency of follow-up

There is limited evidence to guide the ideal follow-up schedule for patients with a history of melanoma. However, it is recommended that the frequency and duration of clinical review should predominantly be based on their staging (Table 1); those with advanced disease require more regular review than those with a lower staging at diagnosis.[8]

Table 1: Recommended frequency of clinical follow-up in New Zealand based on the patient's American Joint Committee on Cancer (AJCC) melanoma stage.[8]

AJCC Stage	General follow-up frequency and duration (Also see: "Considerations for individualising follow-up schedules")
IA	Annually for at least ten years
IB and **IIA**	Every six months for two years, then annually until at least ten years after initial diagnosis
IIB – IIC and **IIIA – IIID**	Every four months for two years, every six months in the third year and then annually until at least ten years after initial diagnosis
IV	Consistent with stage III recommendations plus additional visits as required

N.B. Ultrasound of draining node fields may also be indicated in some patients which may affect the frequency of follow-up (see: "When is laboratory testing or imaging indicated?").

Considerations for individualising follow-up schedules

The follow-up recommendations in Table 1 are consistent with international trends towards a decrease in the frequency and duration of review – a change which is predominantly based on the reliance on consistent patient self-checks in detecting melanoma recurrence.[8, 15] Therefore, while primary care appointments may become less frequent over time, patients must be urged to continue performing their monthly self-checks as part of a lifelong routine.

Participants involved in the Netherlands MELanoma Follow-up (MELFO) study assigned to less frequent primary care follow-up, had significantly lower reports of cancer-related stress than participants who were assigned to a more frequent conventional follow-up;* there were no notable differences in quality of life, number of melanoma recurrences or deaths between both groups.[16] Furthermore, patients may experience a lower level of financial, time and emotional burden from having to attend less frequent appointments. However, it is always important to consider the needs and goals of each patient when deciding on a follow-up schedule, and to tailor it depending on their preference as appropriate.

* In MELFO, the conventional (more frequent) follow-up schedule consisted of three-monthly appointments in the first year, four-monthly appointments in the second year, six-monthly appointments in years 3 – 5 and then annual appointments in years 6 – 10 regardless of disease staging.[16] The experimental follow-up schedule varied depending on the patient's melanoma staging, but in general was less frequent than the convention schedule; it was largely consistent with the recommendations in Table 1, except patients with stage 1B melanoma only had annual appointments until ten years after diagnosis (rather than every six months for two years, then annually for ten years, as detailed in New Zealand guidelines).[8]

When to consider more frequent follow-up. For some patients, regular appointments help to alleviate anxiety and provide reassurance that any potential changes are being tracked and monitored.[17] This may be particularly important if they lack a wide family/whānau or friend support network. Patients with a strong family history of melanoma or a personal history of multiple melanomas, dysplastic naevus syndrome (also known as atypical mole syndrome), multiple naevi (especially > 100 naevi) and/or atypical naevi may also require more frequent review.[8] The addition of digital dermatoscopy significantly enhances follow-up.

When to consider a longer follow-up duration. As the risk of recurrence is greater in the years immediately following diagnosis, the frequency of primary care follow-up tapers off as time progresses. Current guidelines do not specify a need for clinical review beyond ten years after the initial diagnosis if there has been no recurrence.[8] However, it may still be appropriate for some patients to have a longer period of primary care follow-up; this includes patients with stage I melanoma as almost 25% of melanoma-related deaths occur after ten years in this group and higher risk patients, e.g. those aged > 65 years, patients with nodular melanoma or melanoma at high risk sites such as scalp, neck, palms, soles, fingers and toes.[8] Regardless of when this period of review finishes, patients should be encouraged to continue performing regular self-checks at home, and details regarding their diagnosis and follow-up should be well documented in their notes to inform interpretations or decisions made by any other health professionals that are involved in their care in the future.

Assess the patient's wellbeing at each appointment

As with any cancer diagnosis, a diagnosis of melanoma and the ensuing treatment required, can have a significant impact on a patient's quality of life, as well as their mental health and emotional wellbeing.[17] Evidence suggests that emotional

When is laboratory testing or imaging indicated?

Laboratory screening. There is no compelling evidence to support routine laboratory monitoring for detecting melanoma recurrence in asymptomatic patients due to the low specificity of laboratory tests and the corresponding risk of false positive results.[19] In addition, abnormal blood findings are rarely the first sign of metastases.[19] Although serum levels of the S100B protein have been shown to correlate with tumour burden, no improvement in survival outcomes have been demonstrated when S100B-monitoring has been investigated in clinical trials.[19] For patients with stage IV melanoma, an assessment of serum lactate dehydrogenase levels at baseline may have some prognostic value, however, levels can remain "normal" even in patients with late-stage metastatic disease.[7] General laboratory testing is not warranted for most asymptomatic patients at follow-up appointments but may become relevant for monitoring the effects of known recurrence, e.g. liver function testing in patients with liver metastases.[20]

Ultrasound imaging for nodal malignancy. In addition to assessing the patient's history and clinical features at follow-up appointments, six monthly ultrasound imaging of the draining nodal basins should be considered for at least two years following diagnosis in certain patient groups, including those with:[8]

- Stage IB and IIA-C melanoma where sentinel node biopsy is not performed when clinically indicated for any reason, e.g. due to the patient declining
- Sentinel node biopsy-positive stage III melanoma where lymphadenectomy is not performed
- Sentinel node biopsies where one or more lymph nodes were unable to be identified, i.e. non-visualised sentinel lymph nodes
- Where there are concerns about the risk of recurrence, but the patient has characteristics which make clinical examination difficult, e.g. obesity

There are a range of features on ultrasound examination that may indicate possible lymph node malignancy, e.g. longitudinal to transverse diameter ratio of < 2 mm, concentric or eccentric widening of the peripheral cortex, loss or narrowing of the echogenic central hilum/diffuse echogenicity and peripheral vascularity on colour doppler sonography.[8] The success of ultrasound imaging in detecting nodal malignancy is heavily dependent on the experience of the user, however, a combination of multiple features should increase clinical suspicion – particularly if there are clinical signs, e.g. lymph node enlargement on palpation.[19] N.B. Nodal size alone cannot be used to accurately distinguish between benign and malignant nodes as small nodes can have malignant features and benign reactive nodes can be enlarged.[8]

Additional imaging modalities (e.g. chest X-ray, CT and MRI). Chest X-ray as part of routine surveillance for asymptomatic patients is not recommended as it is associated with low rates of melanoma recurrence detection (sensitivity 7.7 – 48% in clinical trials) and a 3.1% risk of false-positive results.[19] Instead, cross-sectional imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), are the key routine investigations recommended for patients with stage II-C melanoma onwards, or when recurrence is suspected based on clinical presentation, history or ultrasound results.[8, 19] There is no international consensus regarding the optimal surveillance regimen for cross-sectional imaging in these higher-risk patients and their use will be co-ordinated in secondary care. Access may differ between regions and will likely be prioritised to patients with more advanced melanoma at diagnosis. Current New Zealand recommendations outline that:[8]

- In asymptomatic patients, routine follow-up with contrast-enhanced CT of the chest, abdomen and pelvis (± neck) can be considered at 3 – 12 monthly intervals in the first three to five years as stratified by clinical stage and time from diagnosis
- If there are equivocal findings on routine CT surveillance, or if there is biopsy-proven local (nodal, satellite or in transit) recurrence or oligometastatic disease, PET-CT should be considered if it would influence a treatment change
- Surveillance high-resolution brain imaging (brain MRI or contrast-enhanced CT head) should be considered in high-risk patients (stage IIC, III [B, C or D] or IV) at 3 – 12 monthly intervals in the first three to five years as stratified by clinical stage and time from diagnosis

Given that some patients with melanoma may be already undergoing six monthly ultrasound imaging of draining nodal basins in primary care (e.g. patients with stage III melanoma if a lymphadenectomy was not performed), routine CT scanning may be redundant or unnecessary as their recurrence is most likely to be nodal. Therefore, a discussion with the patient's secondary care clinician is advised to resolve this potential duplication in imaging.

support from a general practitioner can have a positive effect on a patient's follow-up experience.[17] For Māori patients in particular, acknowledgement of a holistic philosophy/model can be important, such as **Te Whare Tapa Whā** which encompasses physical, psychological, spiritual and family/whānau wellbeing.

Approximately one in five patients report experiencing significant anxiety that persists between appointments related to their diagnosis and the potential for recurrence, and one in ten have associated physical symptoms in the 24 hours leading up to their appointment, e.g. nausea and sleeplessness.[17] Explain to patients that their self-checks and primary care follow-up schedule give the highest probability of identifying recurrence at the earliest possible opportunity,[8] and although remission can never be guaranteed, patients with successfully excised early-stage melanoma can be reassured that metastasis is unlikely.

Ask the patient if they are "ok"

At each appointment ask the patient a general screening question about their mental health and wellbeing, e.g. are they bothered by feeling down, depressed or hopeless, having little interest or pleasure doing things, feeling nervous, anxious or on edge, not being able to stop worrying. If there are concerns, assess further and consider use of a validated patient tool, e.g. **Distress Thermometer**;[8] a similar tool adapted for a New Zealand context is available **here**. Refer to support services such as the Cancer Society or other cultural support networks, as appropriate.[8] Some DHBs offer a Cancer Psychological and Social Support Service (CPSSS) that is specifically aimed at providing support to patients and their whānau who traditionally find it more difficult to access and use such services, e.g. Māori and Pacific peoples, people with socioeconomic disadvantage, people in remote and rural locations and people with significant co-existing physical, social, intellectual or mental health issues. For further information refer to your local HealthPathways.

Consider strategies for improving wellbeing

It may be appropriate to discuss with the patient additional methods to improve their overall wellbeing if they have not considered them already, e.g. a healthy diet, exercise or starting a new activity. There is no consistent clinical trial evidence demonstrating that a specific diet reduces the risk of melanoma recurrence, however, adherence to healthy eating patterns has been broadly demonstrated to reduce the risk of mortality among cancer survivors.[18]

Further information on support for patients with melanoma, see: **https://www.melanoma.org.nz/find-support/information-advisor**

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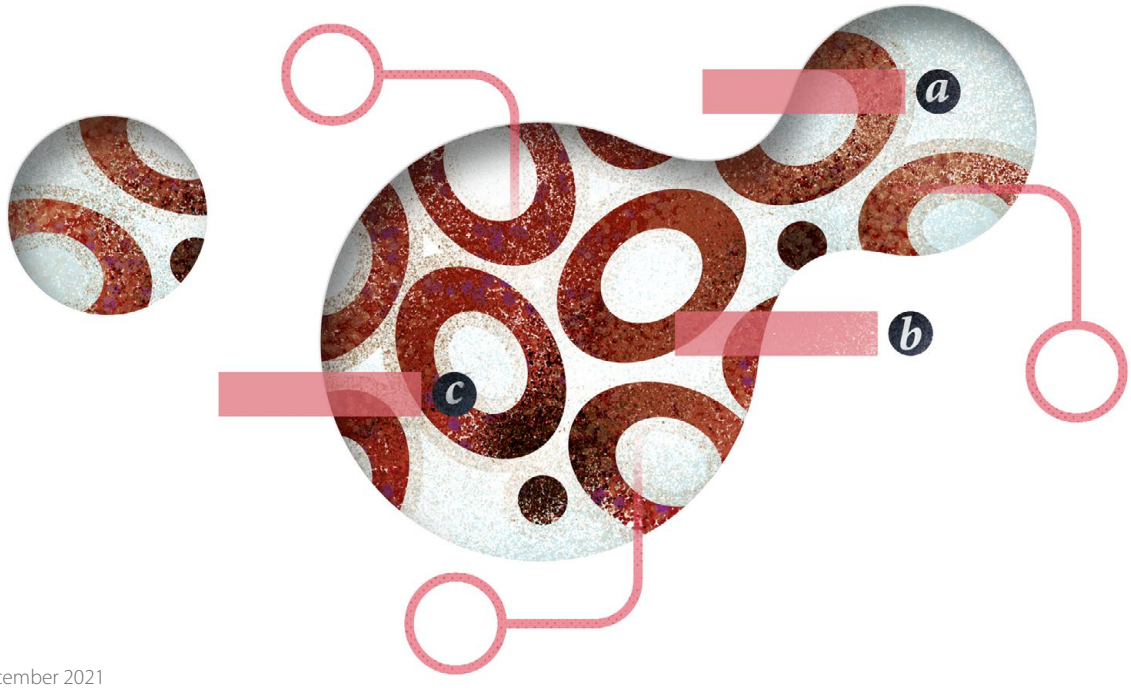

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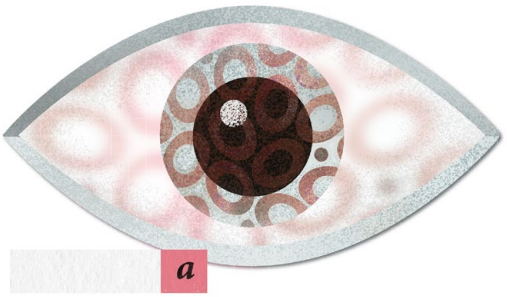

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