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Review

Human dirofilariasis – A potentially significant nematode zoonosis in an era of climate change

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SUMMARY

Dirofilariasis is a mosquito-borne zoonosis caused by several species of the genus *Dirofilaria*. This disease can manifest as nodular lesions in subcutaneous tissues, various structures of the eye, the lungs and/or visceral organs. The *Dirofilaria* species and the vectors responsible for transmitting infection differ among various geographical regions. The most competent reservoirs of infection are domestic and wild canids (for *Dirofilaria repens* and *Dirofilaria immitis*), raccoons (for *Dirofilaria tenuis*) and bears (for *Dirofilaria ursi*), and humans represent aberrant or accidental hosts. Recently, there has been an increasing number of reported clinical cases of dirofilariasis in both animals and humans. It is known that changes in climatic conditions, including increased temperature, relative humidity and rainfall, can contribute to favourable conditions for the development of mosquitoes and larval stages of filarial parasites within their vector. Despite advances in our knowledge of nematodes of the genus *Dirofilaria* and the pathological changes that they can induce in different hosts, many clinicians are unfamiliar with dirofilariasis. Thus, in clinical settings, nodules associated with dirofilariasis are often misdiagnosed as neoplastic lesions. Often, physicians surgically excise such nodules from affected patients, sometimes in very sensitive or difficult-to-reach anatomical locations, which may be accompanied by complications or serious consequences for the patients' health, including a stressful experience in the period from the discovery of a nodule to a definitive diagnosis.
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Introduction

Dirofilariasis is a vector-borne parasitic disease caused by filarioid nematodes of the genus *Dirofilaria,* transmitted by various mosquito species of the family Culicidae (*Aedes*, *Anopheles*, *Culex*, *Ochlerotatus*, *Coquillettidia* or *Mansonia*).[1–4] Of all *Dirofilaria* species, *Dirofilaria immitis* (*D. immitis*) and *Dirofilaria repens* (*D. repens*) are recognised as the most clinically significant human and animal pathogens with a broad geographic distribution worldwide.[5,6] These nematodes naturally infect dogs, cats and/or some wild carnivores, and humans have long been considered accidental "dead-end" hosts, because these parasites do not usually reach sexual maturity in human tissues. However, there are several reports of *D. repens* infection describing circulating microfilariae (first-stage larvae) in the peripheral blood of human patients, tissues surrounding adult worms or within surgically-excised nodules. Until recently, it was proposed that *D. repens* harboured by immunocompromised patients (e.g., with diabetes) develops well, matures and reproduces in humans – as observed in immunocompromised macaques.[7–11] However, a recent review of published clinical cases[12] revealed that most patients from which gravid worms were obtained were immunocompetent, rejecting the proposal.

Currently, 27 cases of human infestations with gravid adult *D. repens* have been reported.[12–17] The presence of gravid females indicates the likely presence of adult stages of both sexes in the human host, even though male worms are usually not reported.[12,18] Taken together, the articles reviewed,[12–17] supported by results of an earlier prospective study which found that ~10% of surgically extirpated nodules contained gravid worms,[19] casts some doubt on the belief that humans are "dead-end" hosts of *D. repens*.

Unlike *D. repens*, infection of humans with a patent *D. immitis* female has only been reported once in the literature.[20] The patient was immunocompromised and died of acute lymphoid leukaemia.[20]

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Other non-canine associated species which occasionally cause human infections include *D. tenuis* (from the raccoon, *Procyon lotor*), *D. ursi* (from the American black bear, *Ursus americanus*), *D. subdermata* (from the North American porcupine, *Erethizon dorsatum*), *D. spectans* (from the Brazilian otter, *Pteronura brasiliensis*) and *D. striata* (from the bobcat, *Lynx rufus*).[21]

As for definitive hosts, animal studies have shown that it takes approximately six months for *D. repens* to fully develop in dogs, and *D. immitis* requires two to three months to develop in subcutaneous tissues before reaching the pulmonary artery. By comparison, *D. tenuis* in the raccoon requires approximately seven months, and *D. ursi* in the American black bear develops microfilaraemia seven to nine months following infection.[22,23] To date, our understanding of the biology of members of the genus *Dirofilaria* has improved, particularly in relation to bacteria of the genus *Wolbachia*, which are endosymbiotic Gram-negative microorganisms present within *Dirofilaria* species.[2] However, there are still many areas, such as parasite migration and development of some unusual subforms of human dirofilariasis, the potential role of this infection in the development of some associated systemic diseases, as well as the efficacy of anthelmintics in the treatment of infection, for which knowledge and understanding are scant.

Dirofilaria affecting humans – biology, risk factors for infection, geographic distribution and proposed pathogenesis

Although the life cycles of some recognised species of *Dirofilaria* (including *D. repens*, *D. tenuis*, *D. ursi*, *D. subdermata* and *D. immitis*) appear to be relatively well characterised (Figs. 1 and 2), the biology and transmission patterns of some operational taxonomic units (OTUs), such as the "Hong Kong" genotype of *Dirofilaria* known to infect humans, are unclear.

It is proposed that female mosquitoes transmit infection(s) to humans by depositing infective third-stage larvae (L3s) on the skin while taking a blood meal. Thereafter, the larvae penetrate into the bite wound and enter the human's body. The further course of infection development differs between *D. repens* and *D. immitis*. In dirofilariasis caused by *D. repens*, L3s migrate to the subcutaneous tissues and undergo two additional moults (from L3 to L4) and then to adults.[7] On the other hand, *D. immitis* L3s moult to fourth-stage larvae (L4) where they, according to animal models, appear to travel between subcutaneous and muscular tissues during early migration within the infected organism. After final moult into sexually immature adults, they continue to migrate through the body, enter the circulatory system, and travel via bloodstream toward the small pulmonary vessels.[24] In contrast to *D. immitis* infection, which usually results in the formation of one or more pulmonary granulomatous nodules, *D. repens* infection may be manifested as either a migrating worm in the subcutaneous tissue or as a granulomatous nodule(s), although there are reports of pulmonary dirofilariasis with this species. Nonetheless, parasite migration, establishment and development in humans are not yet fully understood.[25] For ocular infections, it is hypothesised that microfilariae migrate to the vitreous body and anterior chamber via the bloodstream, where they develop to adults, and that the infestation of extrabulbar structures, such as eyelids, periorbital region and orbit, occurs via the migration of the adult parasite through subcutaneous and subconjunctival tissues.[18,26,27] Current evidence suggests that, following a mosquito bite, L3s migrate into and develop to L4s or adults in subcutaneous tissues, and then migrate to and establish in the lacrimal gland,[28] rather than migrating directly to this gland to develop to adulthood. Irrespective of their location in the body, the parasite-containing nodules can persist for many months or years without causing symptoms,[9] but when they do become apparent clinically (due to increasing size or pain), they raise concern with clinicians as to whether they relate to infectious or non-infectious causes. Often granulomatous or autoimmune diseases, post-traumatic soft tissue lesions or benign or malignant cancers need to be considered as differentials.[2,29] Clearly, molecular genetic tools can assist in the diagnosis of a *Dirofilaria* infection in individual patients but can be also useful for epidemiological investigations.

People who live in or travel to regions endemic for dirofilariasis are at increased risk of infection, and it is proposed that canines are reservoir hosts for human infection.[30] On the other hand, dogs travelling with their owners (e.g., holidays), or imported or rehomed from endemic areas by animal welfare organisations or through legal

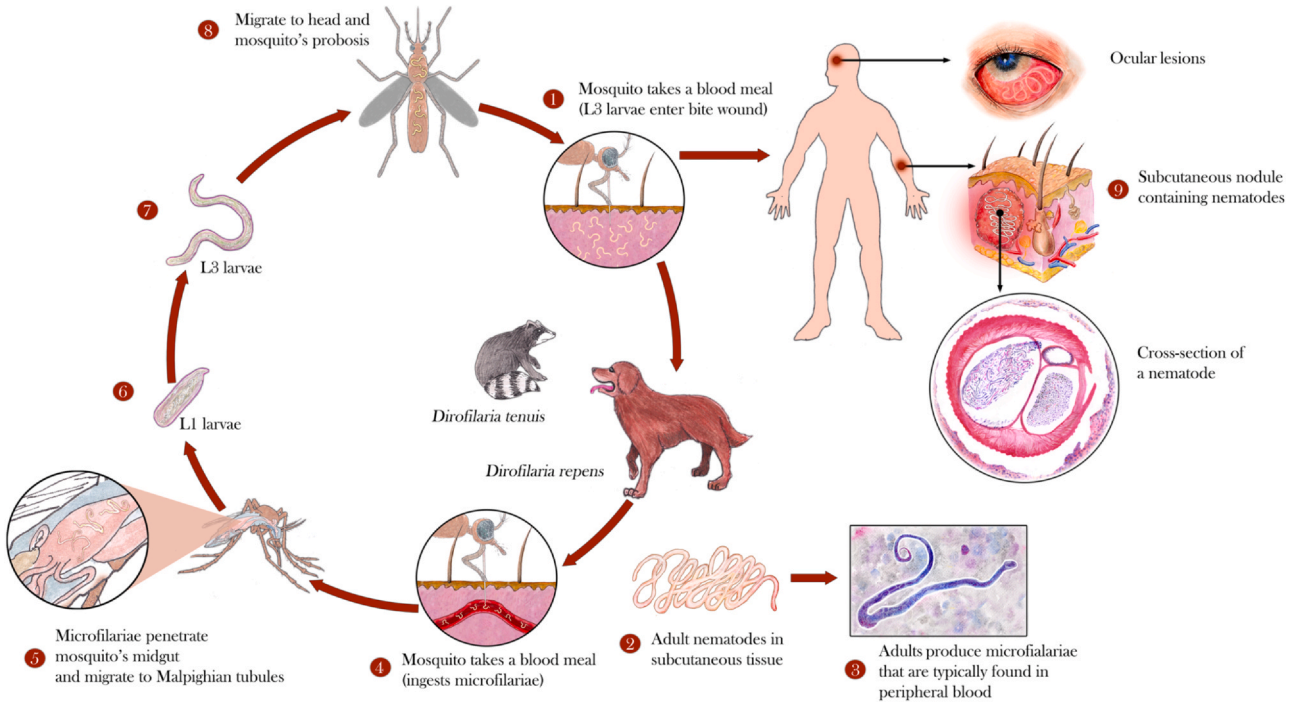


Fig. 1. Life cycle of *Dirofilaria repens* and *Dirofilaria tenuis*.

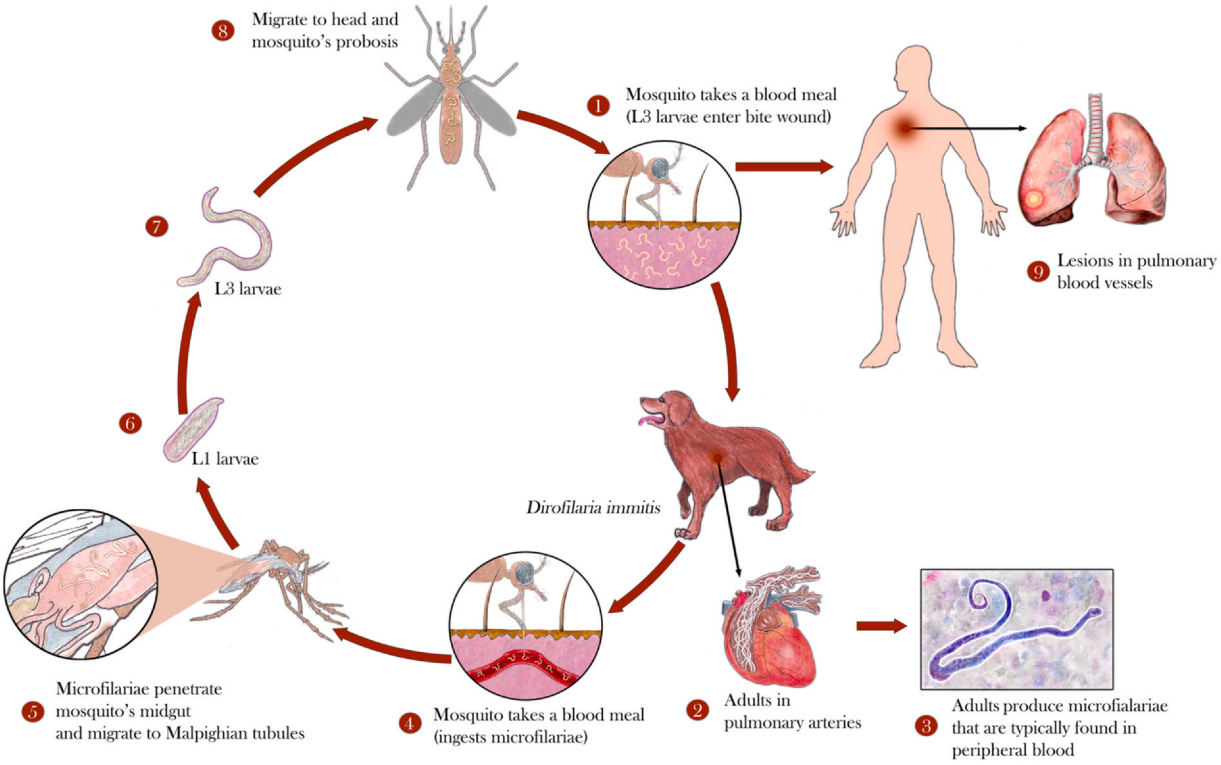


Fig. 2. Life cycle of *Dirofilaria immitis*.

or illegal pet trade, which have not been examined for dirofilariasis by experienced veterinarians and have not received chemoprophylaxis with macrocyclic lactones, could be reservoirs and might introduce the parasite into non-endemic countries.[30–35] In addition, housing near business/recreational activities or visiting areas with natural water sources (ponds, swamps, rivers, canals, lakes and/or water reservoirs), warm-humid climate, adverse meteorological events (e.g., hurricanes or abundant rainfall) and lush vegetation likely represent risk factors for human infection.[36–38] Some epidemiological studies have shown that, in urban environments, housing in multi-story buildings with flooded cellars or areas, potentially frequented by stray dogs, represents a risk factor for dirofilariasis due to mosquito larvae breeding in such locations.[39] However, some countries with small populations of stray dogs have reported a significant incidence of dirofilariasis in such dogs, although molecular studies have not yet established the species of *Dirofilaria* present. This information suggests that, in urban settings, an increased risk of mosquito bites associated with dogs spending nights outdoors may be sufficient to facilitate transmission to humans.[40] In urban settings, buildings can retain heat ("heat islands") during the day and then radiate warmth during the night, favouring the development of mosquito larvae and the transmission of dirofilariasis.[39,41] In rural settings where dirofilariasis is endemic, activities on irrigated agricultural lands represent a likely risk factor for farmers and the community.[41]

D. repens can cause human dirofilariasis in different parts of the world, but most cases have been recorded in Europe and Asia (Table 1). In Europe, the highest prevalence has been established in Ukraine, followed by Russia, Italy and Belarus. In Asia, Sri Lanka and India have the highest prevalence of *D. repens* infection.[6] In people, this infection usually manifests as single, rarely multiple, subcutaneous nodules occurring 2–12 months after infection by L3s. A nodule usually contains only one immature female worm, and nodules with only male specimens or mature parasites are rarely reported.[9,42] However, occasionally more than one *D. repens* adult and the simultaneous presence of adult male and female worms have been recorded in some patients.[43] Subcutaneous nodules are most commonly detected in exposed parts of the body, such as head and neck regions, arms, thoracic wall and lower extremities,[44] and orbital and periorbital areas.[45–47] Evidence indicates that nodules form near mosquito bites, but larvae can migrate to other locations until encapsulated within a granulomatous lesion, although further migration might occur.[1,48,49] *D. repens* has an ability to migrate up to 30 cm in 2 days,[50,51] although it can travel even further in subcutaneous tissues (e.g., from the lower limbs to the head or from one side of the body to the other), possibly due to their ability to evade host immune responses.[1,19,50]

A higher prevalence of *D. repens* infection has often been recorded in middle-aged and older patients (> 50 years of age), including those with known, patent infection.[12,13,18,37,45,46,71,72,73] Although patent *D. repens* infection appears to be more common in male patients,[12–17] females seem to be affected more by dirofilariasis than males.[45,46,71,72,73] Interestingly, in Sri Lanka, unlike other Old World countries, *D. repens* infection is most common in children of < 9 years of age, particularly in genital and perianal regions.[52] A possible explanation for the variable patterns of *D. repens* infection linked to age or sex may relate to differing behaviours, outdoor activities, habits and/or clothing preferences.[30,39,74]

D. tenuis, *D. ursi* and *D. subdermata* can each cause subcutaneous and ocular dirofilariasis in North America (Table 1).[75] Human cases in northern USA and in Canada have generally involved *D. ursi* or *D. subdermata*.[75] On the other hand, in southeastern USA, the majority of cases have been attributed to *D. tenuis*.[76,77] The latter species is endemic to Florida, particularly in its southern region, where most (80%) cases are found in people visiting this region.[75,77]

D. immitis infection usually causes pulmonary dirofilariasis in humans, and is most prevalent in Japan (254 cases)[78] and the Americas (175 cases)[5] (Table 1), particularly subtropical and tropical regions, where transmission can occur almost year-round.[3] This infection has been recorded to a much lesser extent in Europe and

Table 1
Dirofilaria species causing human dirofilariasis.

Dirofilaria sp.	Vectors	Definitive hosts	The most prevalent regions for human dirofilariasis	First described human case	Number of reported human cases	Sex predilection in human dirofilariasis	Population age group at higher risk of human dirofilariasis	The most common anatomical location of infection	The presence of microfilariae in humans	References
Dirofilaria repens	*Aedes* spp., *Culex pipiens*, *Anopheles* spp., *Ochlerotatus* spp., *Coquillettidia* spp., and *Mansonia* spp.	Domestic dog, wolf (*Canis lupus*), red fox (*Vulpes vulpes*), Eurasian badger (*Meles meles*), humans[a]	Mediterranean countries (Italy, southern France, Greece, Spain) and eastern European countries (Ukraine, Russian Federation and Belarus)	1566, southern France	> 1500	Female	> 50 years and < 9 years of age[b]	Subcutaneous tissue of facial and ocular region and subconjuctival space	Yes, 27 reported cases	1,4,7,12–17,52,53
Dirofilaria immitis	*Aedes* spp., *Anopheles* spp., *Culex* spp., and *Ochlerotatus* spp.	Domestic dog and cat, brown bear, jackal (*Canis aureus*), Iberian wolf (*Canis lupus signatus*),	South and North America and Japan	1887, Rio de Janeiro, Brazil	> 450	Male	40–59 years	Pulmonary small-calibre vessels	Yes, only one reported case	2,4,20,29,54,55
Dirofilaria tenuis	*Aedes taeniorhynchus*	Raccoon, (*Procyon lotor*)	Southeastern USA	1952, Florida, USA	~50	Female	30–39 and 60–69 years	Subcutaneous tissue of upper extremities and ocular region and subconjuctival space	Yes, two reported cases	4,56,57
Dirofilaria "Hong Kong" genotype	Unknown	Unknown	Kerala, India and Hong Kong, China	2012, Hong Kong, China	~20	Unknown (there is no information on sex for more than half of the patients)	Unknown (there is no information on age for more than half of the patients)	Subconjunctival space	No	48,58–67
Dirofilaria ursi-like sp. (*D. ursi* and *D. subdermata*)	Black flies (Simuliidae)	Kamchatka brown bear (*Ursus arctos beringianus*), brown bear (*Ursus arctos*), Japanese black bear (*Ursus thibetanus japonicus*), and American black bear (*Ursus americanus*) North American porcupine (*Erethizon dorsatum*)	Northern USA and Canada	1963, Washington, USA	~13	Female	20–29 and 40–49 years	Subcutaneous tissue of head and breast	No	4,42,68
Dirofilaria spectans[c]	Unknown	Giant otter (*Pteronura brasiliensis*), tayra (*Eira barbara*), Neotropical otter (*Lontra longicaudis*)	Unknown	1953, Rio de Janeiro, Brazil	1	Unknown	Unknown	Unknown (the parasite was extracted from the digital artery in reported case)	No	4,69
Dirofilaria striata[c]	Unknown	Cougar (*Puma concolor*), margay (*Leopardus wiedii*), ocelot (*Leopardus pardalis*), bobcat (*Lynx rufus*), and Florida panther (*Puma concolor coryi*), domestic dog and cat	Unknown	1990, North Carolina, USA	1	Unknown	Unknown	Unknown (the parasite was extracted from the eyelid in reported case)	No	4,70

[a] Twenty-seven recorded human cases in whom the presence of microfilariae has been detected suggest the potential possibility of involving humans as definitive hosts.
[b] Data about Sri Lanka which is different compared to other parts of the world.
[c] Only single cases have been reported in the literature to date.

Australia, and sporadic cases have been recorded in India, New Zealand and Tunisia.[5] Inside the permissive definitive host (a canid), *D. immitis* L3s develop subcutaneously to L4s within 23 days, after which they moult and develop to the juvenile adult stage (between days 50 and 70), and then migrate (via the blood stream) to the pulmonary artery (usually by day 70) where they mature fully and reproduce within 6 to 7 months.[24,79] However, in humans, *D. immitis* L3s do not develop to mature, reproductively active adults.[54] Thus, humans are non-permissive hosts, and the infection is amicrofilaraemic.

D. immitis L4s are exposed to cellular and humoral immune responses (e.g., polymorphonuclear leukocytosis, monocytes, T cells, and NK cells; complement factors, antibodies; and cytokines/chemokines, or other soluble factors) that can kill them.[1,80] If the host's immune system does not destroy the parasite in the skin or during its 'migration' via the bloodstream, L4s reach the fine branches of the pulmonary artery and develop to the adult stage, induce vasculitis and then die. Such larvae release antigens that cause endarteritis and localised pneumonitis, followed by nodule formation (spherical "coin lesions") within lung parenchyma, contrasting the characteristic radiological appearance of embolic infarction, characterised by wedge- or pyramidal-shaped lesions. Coin lesions (singular or multiple) are usually located at the lung periphery and can remain stable in size for years.[42,81,82] Although there is no evidence of a specific affinity of *D. immitis* for the pulmonary vasculature in humans,[54,82] this species usually enters the venous circulation, but might occur also in arterial vessels.[82]

Pulmonary dirofilariasis caused by *D. immitis* has been reported to predominate in adult male patients (40–59 age group), whereas this disease is rare in children.[29,54] This difference may relate to variation in parasite biology, immunologic responses, hormonal status and/or frequency of radiographic examinations in distinct age groups, enabling a diagnosis.[83] A "coin lesion" in a child is more likely to be interpreted as a Ghon complex or histoplasmosis, which is why it is less often surgically removed and sent for histological examination.[84] In addition, symptomatic cases of pulmonary dirofilariasis are recorded somewhat more in women, which may be explained by the tendency of males to underreport disease(s).[85] Based on current evidence, there appears to be no particular racial predisposition to *D. immitis* infection,[85,86] and seroprevalence in humans is higher in people in underprivileged communities, where health care and measures to prevent transmission from canines to humans are absent.[38]

The sex bias in the number of subcutaneous dirofilariasis (associated with gravid nematodes) and pulmonary dirofilariasis cases toward male patients suggests that immunological and/or hormonal factors might play a significant role, contrary to earlier opinion.[85] Recent studies[87,88] have highlighted that both innate and adaptive immune responses differ between males and females, potentially associating with susceptibility to infectious and non-infectious diseases (immune-mediated and cancers). In addition, higher concentrations of androgens, such as dihydrotestosterone and testosterone, in post-pubertal males usually suppress immune responses.[89] Based on this information, it is proposed that adult males have a reduced immunological capacity to eliminate *Dirofilaria*, enabling an extended survival of the parasite at the inoculation site, sexual development and maturation of worms (*D. repens*) and/or migration to pulmonary blood vessels (*D. immitis*).

The "Hong Kong" genotype of *Dirofilaria*, first described in 2012 as novel species of *Dirofilaria* recorded in human patients and in stray dogs in Hong Kong,[58] is proposed as a causative agent of subcutaneous or subconjunctival dirofilariasis in humans with a likely reservoir in canines (Table 1).[90] To date this genotype has also been seen in subcutaneous nodules in patients from India and Thailand, in patients from Germany and Austria (after travel to India),[4] and in the subconjunctival space of one patient in Australia who migrated there from Sri Lanka.[90] Despite these reports, the significance and role of this genotype as a pathogen in animal hosts is still largely unknown.[58] Currently, in the absence of a precise morphological description of this genotype, it is considered as a *nomen nudum* by the scientific community.[4]

Clinical presentation and challenges

Human dirofilariasis can be classified into three main clinical forms, based on the location of the nodular lesion(s): ocular, subcutaneous and pulmonary, although this classification does not encapsulate all forms reported in the literature to date.[29] However, based on existing knowledge, and for convenience, dirofilariasis of soft tissues, body cavities and the viscera can be assigned to the subcutaneous form.[7]

Ocular dirofilariasis

Dirofilaria species can cause serious damage to the external and internal structures of the eye via different processes/mechanisms - directly, from damage to host tissues caused by the invasion of the parasite or ectopic parasitism by larval or adult stages of *Dirofilaria*.[91] To date, ocular dirofilariasis has been linked to *D. repens* (n = 137 cases), *D. immitis* (n = 13), *D. tenuis* (n = 12), the "Hong Kong" genotype of *Dirofilaria* (n = 7) or *D. striata* (n = 1),[90,92–95,59,60,96] although molecular methods were not consistently used to confirm the specific identity of worms found.

This form of dirofilariasis occurs most often in individuals over the age of 40 (~49 years), with almost equal representation in both sexes. Of the 186 documented cases, the right eye was involved in 73 cases (39.2%), while the left eye was affected in 84 cases (45.2%), and three cases (1.6%) were bilateral.[96]

Ocular dirofilariasis might present as a periorbital, subconjunctival, orbital or intraocular infection.[97–99] Based on analyses of published cases of ocular dirofilariasis, the parasites were mostly located under the conjunctiva, in eyelid and periorbital soft tissues, although migration into the peri-, intra- and/or retro-ocular spaces was observed in some instances.[21,71,100,101]

The commonest clinical manifestations of subconjunctival dirofilariasis are conjunctival hyperaemia, burning, itching, ocular pain, epiphora, photophobia, blepharospasm, swelling of the eyelids and/or foreign-body sensation in the eye, leading to pain and concern.[27,71,102–104] Therefore, patients with a subconjunctival form of ocular dirofilariasis usually seek medical care early.[105] However, upon initial ophthalmological examination, the aforementioned symptoms and signs are often mistaken for allergic conjunctivitis, particularly by inexperienced ophthalmologists.[71] On the other hand, patients with periorbital dirofilariasis usually present with a gradually increasing cystic, sometimes painful eyelid swelling or periorbital oedema which may be associated with redness, mild itchiness, tenderness, sensation of a foreign body moving in the eyelid and/or varying degrees of ptosis.[106–113] Rarely, an elevated local skin temperature can also occur.[106] When live worms are located in an eyelid, a diagnosis may be more rapid because of their migration through the thin, periocular soft tissues,[114] while motile worms, cystic or solid mass-like lesions are directly visible subconjunctivally using a slit lamp due to the transparency of the bulbar conjunctiva.[72,91,115]

Orbital infection can involve the lacrimal gland,[28,97,116] sub-Tenon's space[117,118] and extraocular muscles (such as the superior,[119] medial[120] and lateral rectus muscle,[98] and/or levator palpebrae muscle[111]), or can exhibit as orbital soft tissue tumour-like lesions.[114,121–124] In patients with orbital dirofilariasis, an initial examination usually reveals the presence of a well-defined, palpable dense mass, deep in the eyelid or in the periorbital region, sometimes associated with pruritus and reddening of the overlying

skin.[102,112] The mass can disappear within weeks, and the swelling of the eyelid can relate to the formation of a dense nodule in the inner part of the orbit.[112] During the clinical course, the migration of a worm deep into the orbital tissue can be accompanied by exophthalmos and/or diplopia, particularly in cases where the newly formed inflammatory nodule leads to a displacement of the orbital muscles or is localised in the retrobulbar space.[112,122] Dirofilariasis of the lacrimal gland, as a rare and non-specific subform of orbital dirofilariasis, is usually characterised by the presence of a well-defined, usually firm mass in the anterior, superotemporal region of the orbit and is often associated with swelling, redness, conjunctival congestion with chemosis and varying degrees of ptosis.[28,97,117] In some instances, bacterial or fungal secondary infections of orbital lesions have been reported.[112,122]

In intraocular cases, *Dirofilaria* worms have been detected in the sclera,[103] retina,[125] anterior chamber,[126–128] crystalline lens,[129] vitreous cavity[130] and over the optic disc.[131] Dirofilariasis of the anterior chamber may be manifested by corneal oedema, episcleral hyperaemia, ocular pain and/or redness, iritis and/or visual impairment.[126–128,132] In one unusual human case,[126] multifocal choroiditis in the posterior pole, with retinal pigment epithelium tracts and chorioretinal scars, was also described. On the other hand, the presence of *Dirofilaria* worms in the vitreous chamber can be associated with redness and/or ocular discomfort, the appearance of floaters and motile “snake-like” shadows, vitritis, chorioretinitis and visual impairment.[100,130,133–136] In addition, in some instances, extensive chorio-retinal damage, characterised by the presence of vitreous floaters, hyperaemic optic disc, epiretinal membrane, extensive retinal pigment epithelium atrophy, mottling and defects in the visual fields, has been reported.[137] In an exceptional case of retinal dirofilariasis, a round, preretinal haemorrhage along the superonasal retinal artery was observed upon an ophthalmoscopic fundus examination, as well as numerous subretinal hypopigmented tracks in the superior retina.[125]

Intraocular and retroocular dirofilarioses are very rare, but can be challenging to diagnose due to the profound location of the worms and the relatively non-specific and unusual clinical presentation. Thus, these infections can be accompanied by significant damage to the delicate structures of the eye, leading to negative physical and psychological effects in patients.[138] Potential complications that can occur as a result of the continued presence of worms in the eye include impaired vision, floaters, glaucoma, retinal detachment, crystalline and vitreous opacity, loss of visual acuity and sometimes blindness.[72,139]

A very unusual case to note is dirofilariasis of the pterygium in a patient from Thailand.[140] Pterygium is a fibrovascular overgrowth of the subconjunctival tissue, triangular in shape, and encroaching to the cornea in the medial and lateral palpebral fissure.[141] Apart from this case, there is no other, similar case reported to date.

Due to marked variation in clinical manifestation, ocular dirofilariasis is often under the guise of other ophthalmological, dermatological, surgical, oncological or infectious diseases, which makes a definitive diagnosis challenging.[142] *Dirofilaria* infections in subconjunctival tissues can often mimic allergic or bacterial conjunctivitis,[105] loaiasis,[143] and scleritis,[18,92] whereas infections of the eyelid can be misdiagnosed as subcutaneous cysts or granulomata,[115] chalazion[144] or hordeolum.[145] In cases with the periorbital form of dirofilariasis, differential diagnoses include an epidermoid or dermoid cyst, sarcoidosis, idiopathic orbital inflammatory disease, preseptal cellulitis, infectious abscess, and benign (most often lipoma and fibroma) and malignant tumours.[105,111,146] On the other hand, in patients with *Dirofilaria* infection presenting as an orbital mass, differential diagnoses might include neoplastic, granulomatous and/or inflammatory diseases, pseudotumors and/or other parasitoses with potential orbital involvement, such as cysticercosis, echinococcosis or onchocerciasis.[122] If the lesions detected are painless, lymphoma or metastatic processes are most commonly suspected.[147,148] Moreover, a suspicion of orbital metastasis is particularly high in patients with a history of cancer(s).[117] Dirofilariasis of the lacrimal gland can mimic a lacrimal sac mucocele,[91] as well as different types of vasculitis, granulomatous inflammation, such as Wegener granulomatosis, sarcoidosis, sclerosing inflammation, Sjögren syndrome or autoimmune diseases.[118]

It is important to emphasise that, despite improved understanding of the clinical features of inflammatory eye diseases and advances in diagnostic testing, clinicians should be suspicious of parasitic infections in patients thought to have inflammatory eye involvement.[149] In addition to dirofilariasis, other helminth infections, such as angiostrongyliasis, bancroftian and brugian ocular filariasis, baylisascariasis, loiasis, onchocerciasis, thelaziasis, toxocariasis and trichinosis, may also affect different eye structures.

For ocular angiostrongyliasis, occasionally reported in tropical or subtropical areas, the worm may migrate directly to the eye without brain involvement.[150] Ocular symptoms typically occur between two and eight weeks after consuming raw *Pila* snails and include eye redness, pain and disorders in visual acuity which ranges widely.[149,150] In some patients, severe impairment of visual acuity has been reported, lasting 4 days to 8 weeks, often 2–3 weeks.[149]

Bancroftian and brugian human ocular filariases, mostly reported in South-East Asia, are rare and can affect various structures of the eye. These infections may cause retinal inflammation, vasculitis, vision loss, panuveitis and secondary glaucoma.[149] *Baylisascaris procyonis*, the raccoon roundworm, in North America, has been linked in humans to diffuse unilateral subacute neuroretinitis and choroidal infiltrates in children.[149] *Loa loa*, also called “African eye worm”, is transmitted to humans via adult female *Chrysops* flies. The ocular form of loiasis can be caused by both microfilariae and adult worms. Worms can be seen intermittently under the conjunctiva of infected people. In addition, a transient and migratory oedema (“Calabar swelling”) is usually present on the periphery of the eye(s).[149,151] Onchocerciasis, also known as the African river blindness, is, after trachoma, the second most important cause of infectious blindness worldwide.[152] In this infection, microfilarial migration through ocular structures and the host’s immune response are responsible for most of the clinical manifestations, such as punctate keratitis, sclerosing keratitis, iridocyclitis, chorioretinitis and optic atrophy. Pupil distortion and exudate coverage have also been described in some cases.[149,152]

Thelaziasis, caused by “the Oriental eye worm” *Thelazia callipaeda*, is transmitted by drosophilid flies that feed on lacrimal secretions[153] and presents in humans with symptoms including epiphora, conjunctivitis, keratitis, corneal opacity and ulcers. Both adult and larval stages are responsible for ocular disease.[149]

Ocular toxocariasis is caused by the migration of *Toxocara* larvae via circulation into the posterior segment of the eye. When the larva enters the eye, an immune reaction can occur, resulting in inflammation and permanent scarring. This form of *Toxocara* infection is usually unilateral and may present with decreased vision, eye redness, pain, floaters or photophobia.[154] Finally, with only few reported cases, ocular trichinosis is rare, presenting with facial oedema (particularly around the eyes), conjunctivitis and exophthalmos.[149]

Interestingly, there is some evidence of a link between dirofilariasis and mucosa-associated lymphoid tissue (MALT) lymphoma of the lacrimal gland.[155] Although this link is still unclear, it is proposed that a chronic inflammatory response in the patient results in an accumulation of extranodal lymphoid tissue and that excretory/secretory molecules (including those extracellular vesicles, EVs) from *Dirofilaria* contribute to inducing non-Hodgkin lymphoma. It has also been suggested that the bacterial endosymbiont *Wolbachia* might play a role in the development of MALT lymphoma, warranting detailed exploration.[155] Other chronic diseases caused by

worms, such as *Spirocerca lupi* in canids,[156] *Schistosoma haematobium* in the urogenital tract[157] and species of *Opisthorchis*[158] and *Clonorchis*[159] in the liver of humans, are known to be linked to particular cancer types, including osteosarcoma or fibrosarcoma; squamous cell carcinoma; and cholangiocarcinoma or hepatocellular carcinoma, respectively.[156–159]

Subcutaneous dirofilariasis

In patients with subcutaneous dirofilariasis, nodules can occur in various human body areas and tissues, affecting the superficial tissues of the facial regions, periorbital and perioral tissues,[7] scalp,[45,68,160,161] forehead,[18,36,45,162] skin of the upper and lower extremities[163,164] and soft tissues of the hand or fingers,[7] subcutaneous tissue of the neck, anterior[49] and posterior thoracic walls,[165] abdominal wall,[166] and, to a lesser extent, mucosal and submucosal tissues of the oral cavity.[167] Other, less common predilection sites include external male genital regions, such as scrotum and penis, as well as the breasts of females.[7] In some cases, however, the parasites may also reach deeper tissues and structures,[7] such as lymph nodes,[164,168–172] muscles,[102] subperiosteal spaces,[18] retrosternal areas,[173] the abdominal cavity,[174] mesentery,[175] omentum,[176] peritoneum,[164] gastrosplenic ligament[177], liver,[86] pancreas,[178] intestinal wall,[179] inguinal hernia sac,[176] spleen,[180] pelviureteric junction and upper ureter,[181] urinary bladder,[182] ovaries,[183] fallopian tube,[184] uterus,[185] testicles,[186] epididymis,[187] spermatic cord,[188] and even the duramater[189] and intracerebral space.[190]

Clinical manifestations resulting from subcutaneous nodules linked to dirofilariasis depend on their localisation and can include local irritation, erythema and/or pruritus.[7] Sometimes, urticaria[191,192] or genuine creeping eruption, the characteristic clinical sign of cutaneous larva migrans syndrome (small reddish papule that progresses to a serpiginous pruritic rash) may also occur.[9,51,193,194] However, in rare cases associated with a pronounced local immune/inflammatory response, the nodules may appear as an ulcerated tumour-like lesion,[195] necrotic lesion[196] or an abscess, accompanied by mild systemic reactions, such as elevation of body temperature and mild eosinophilia.[7] An abscess may rupture spontaneously to the surface, if digitally manipulated, or accidentally/intentionally punctured, with consequent drainage of purulent material.[112,162] Furthermore, cases of spontaneous evacuation of a nematode from the suppurating nodule, together with pus, or induced by the patient themselves (i.e. by squeezing the nodule or vigorous rubbing), have also been described.[72,162] Very rarely, more serious systemic manifestations, such as nausea, headache, weakness, fever, reactive arthritis or lymphadenopathy might occur[7,76,112,197], while exceptional cases of eosinophilic meningitis[61,198] and meningoencephalitis[48] have also been described. In addition to microfilariae that can cross the blood-brain barrier and cause neurological symptoms,[48] migrating worms appear to be responsible for triggering generalised immune responses involving the central nervous system.[61]

Although the frequency of published reports of subcutaneous dirofilariasis has increased recently,[49] achieving an accurate diagnosis, based on the clues obtained during a clinical examination, has been a challenge undertaking, sometimes even for experienced physicians. In most cases, disease goes unnoticed, and patients usually seek medical help after accidental palpation of a subcutaneous nodule.[71] In daily clinical practice, due to the absence of characteristic signs, the typical presentation of subcutaneous dirofilariasis is very often misdiagnosed as an infected or non-infected sebaceous cyst, ruptured dermoid cyst, abscess, fungal infection, tuberculosis, cutaneous fascioliasis, thrombophlebitis, enlarged lymph node, foreign body granuloma, fat necrosis, sarcoidosis, idiopathic pseudotumor, haematoma, adenoma, hamartoma, neurofibroma, lipoma, schwannoma or basal cell carcinoma.[102] Moreover, in specific cases, depending on the anatomical location and the type of tissue in which the nodule is detected, the differential diagnosis of subcutaneous dirofilariasis in humans might include a wider range of subcategories of pathological entities. Currently, five subcategories of subcutaneous dirofilariasis are proposed:

Dirofilariasis of the oral cavity

The oral cavity is a unique and complex structure, consisting of several different anatomical units (including the lips, tongue, floor of the mouth, buccal mucosa, upper and lower gingiva, teeth, retromolar trigone, and soft and hard palates), which function together to efficiently perform various physiological functions.[199,200] In addition, there is no other body cavity that shares such a close connection with the external environment.[201]

Although dirofilariasis of the oral cavity is a rare clinical entity (27 cases reported to date), it occurs most often in persons of more than 40 years of age, and appears to have a female predilection.[167,202–204] The commonest cause of this form of dirofilarasis is chronic *D. repens* infection, although the species of parasite was indeterminate in multiple cases.[205–208] A unique case of oral mucosa infection with *D. tenuis* has been reported, but without molecular-diagnostic confirmation.[77] In most published cases, a single dead or degenerating nematode was detected in surgically-excised intraoral lesions, although live worms were very rarely observed.[167,209,210] Lesions are usually found in the buccal mucosa, followed by the buccal vestibules, lips, submucosa of the tongue and, in individual cases, regions above the left angle of the mouth, in the root of a tooth, and the tissue of the soft palate and isthmus of the fauces.[72,167,203,204]

This subtype of dirofilariasis is thought to result from nematode migration from the initial site of entry, such as the subcutaneous tissue of the face, inward to the oral mucosa.[59,191,199,200].

Patients with oral dirofilariasis often present to the dentist, oral or maxillofacial surgeons with a solitary, usually painless, mobile, firm, slowly growing submucosal nodule measuring ~0.5–2.5 cm in diameter. The development of a nodule is preceded by a swelling of the mucous membrane, which can be intermittent in nature,[167,203,206,209-211] and can be associated with tenderness,[212] pain,[194,207,208] itchiness and fever. Interestingly, the latter two manifestations appear to express during the night,[202,206,211] most likely due to an increase in the activity of the parasite. In some cases, diffuse extraoral swelling in the middle and lower thirds of the face can cause varying degrees of facial asymmetry.[211,212]

From a clinical perspective, oral dirofilariasis can mimic different pathological entities, such as an infected epidermoid cyst,[213] granulomatous disease,[209] lymphadenopathy,[205] cysticercosis,[202] abscess, allergic reaction,[212] mucocele,[205] traumatic neuroma, herniation of buccal fat,[214] mesenchymal benign or malignant process,[215,216] or glandular benign or malignant neoplasm with an inflammatory reaction, sometimes including secondary infections.[208,215,216] In patients with ultrasonographically-detected, hypoechoic lesions, associated with patches of calcification, oral dirofilariasisis sometimes confused with calcified lymph nodes, tuberculosis, sialolithiasis, phleboliths or traumatic ossifying myositis.[206,211]

Dirofilariasis of the lymph nodes

With only 12 isolated cases described in the literature, lymph nodes continue to represent an atypical localisation for human dirofilariasis.[217] Although rare,[217] this subcategory of subcutaneous dirofilariasis has been described in all clinically relevant types of lymph nodes located near the surface of the skin, including the submandibular area,[72] neck,[58,218] supraclavicular,[170] axillary[171] and inguinal regions.[72,168,169,217,218]

In one case in a 60-year-old woman, a nematode of the genus *Dirofilaria* was aspirated from a pseudotumoral para-aortic mass of lymphatic origin, and subsequently identified as an adenolymphocele.[219] Clinically, dirofilariasis of the lymph node(s) usually manifestes as an enlarged (> 1 cm in diameter) painless, non-inflamed or painful inflamed node(s) associated with hyperaemia and oedema of the overlaying skin – sometimes accompanied by fever and/or ipsilateral lymphadenopathy.[169,170,172,217]

Dirofilariasis of the skeletal muscles

To date, some unusual cases of muscular dirofilariasis have been reported, although some common parasites of the musculature of humans and other animals include *Trichinella* spp., *Taenia solium* and *Toxoplasma gondii*. In addition to extraocular muscles,[98,111,119,120] nodules linked to dirofilariasis have been identified in the orbicularis oculi,[18] temporalis,[220–224] masseter,[225,226] pectoralis major,[227,228] brachioradial[229] and triceps surae muscle.[230] An analysis of published cases indicates that patients with intramuscular dirofilariasis usually present with gradually increasing and chronic swellings. If marked inflammation is present, these swellings may be associated with discomfort, itchiness and/or pain.[18,221,224,225,229] In dirofilariasis of the temporalis muscle, trismus, deviation of the mouth to one side, mild swelling over the ipsilateral temporomandibular joint[222] and submandibular lymphadenopathy,[223] and systemic symptoms such as dizziness, tingling paraesthesia, nausea, vomiting and/or severe headache might occur.[222,223] In some cases, intramuscular dirofilariasis might manifest as a nodule without additional symptoms/signs.[223] In others, a soft tissue mass caused by dirofilariasis might be fixed to underlying structures, which may arouse a suspicion of a cancerous process.[221] On occasions, temporal dirofilariasis may mimic a neurological disorder, such as an intracranial haemorrhage and ischaemic lesion, the prodromal phase of shingles (Herpes zoster), or may resemble temporal arteritis, in association with a local inflammatory process.[224]

Dirofilariasis of atypical locations – soft tissues of the upper extremities

Atypical locations of subcutaneous dirofilariasis on the upper extremities require particular attention, considering the potential diagnostic dilemmas that can arise during the clinical examination of patients by orthopaedists, plastic surgeons or rheumatologists. As the elbow, wrist and hand represent complex networks of bones, muscles, nerves, tendons, ligaments and blood vessels, a detailed clinical examination approach is required.

Published information reveals that *D. repens* is most frequently identified in atypical locations,[231–235] although rare cases of *D. immitis*,[236] *D. tenuis*,[237] and *D. spectans* infection[69] have been reported. However, in most cases, diagnosis was based exclusively on the morphological identification of the worms from nodules.

In one case, a patient presented at an orthopaedic clinic in Poland with pain and swelling of the left elbow, and bursitis was established as the initial diagnosis.[231] Consequently, a bursa puncture was performed and a steroid (betamethasone) administered. However, contrary to an expected improvement, the patient returned after a week with more severe symptoms, suggesting that a second bursa puncture was indicated. During the procedure, a nematode was aspirated from the synovial membrane sac and identified as *D. repens* using microscopic and molecular tools.[231] In cases where the application of first-line therapy (i.e. physiotherapeutic methods, NSAIDs, corticosteroids and antibiotics) does not or only slightly reduces symptoms, dirofilariasis should be considered as a differential diagnosis, particularly in areas endemic for specific *Dirofilaria* species.

In another atypical case from Florida, the presence of a nodule on the left forearm, near the superficial branch of the radial nerve, which contained degenerating *Dirofilaria*, caused significant motor and sensory deficits - stiffness and weakness of the thumb, index and middle fingers, as well as most of the left arm. The underlying mechanism for this neurological disorder was extensive subcutaneous inflammation that spread beyond the nodule, causing radial neuritis in the patient. Clinically, the nodule was painless and raised concerns about a neurofibroma. Following the surgical excision of the lesion, all clinical manifestations quickly subsided.[238]

Depending on the initial inflammatory (erythematous nodule painful upon palpation) or non-inflammatory presentation (asymptomatic nodular lesion or soft tissue oedema) and specific location (e.g., the tissues above the tendons[239] or around the joints,[240] tendinous sheath,[241] palmar subcutaneous tissue[233,234] or the lumen of digital artery),[69] nodules linked to dirofilariasis in soft tissues of the hand may clinically mimic tendonitis, tenosynovitis, ganglion, giant cell tumour, foreign body granuloma and Raynaud's 'phenomenon'.[233–236,69,239–242] In addition, due to the presence of a local mass effect on the median nerve, a growing subcutaneous nodule in the carpal tunnel associated with dirofilariasis might resemble carpal tunnel syndrome, particularly if the Phalen's test is positive.[237,243]

Dirofilariasis of the reproductive tract and female breast

Human dirofilariasis is rarely associated with the urogenital tract, particularly in women, but it should be listed as a clinical entity by urologists and gynaecologists, because, in practice, it is often not considered as a differential diagnosis.[18,244,245] To date, cases of dirofilariasis affecting the scrotum,[246] penis,[62] testicle,[186] epididymis[245] or spermatic cord[188] in men and ovary,[183] fallopian tube[184] and uterus[185] in women have been reported.

Dirofilaria infection of the genital organs probably occurs following subcutaneous migration of the L4 or adult stage from the primary site of the mosquito bite.[246] A lower body temperature in these areas and/or a tropism of *Dirofilaria* to higher concentrations of sex hormones might be factors responsible for this predilection.[7] Some published evidence suggests that the frequency of genital localisation of *Dirofilaria* in the male population is 2–4% worldwide,[244] with the exception of Russia and Sri Lanka, where the prevalence of genital dirofilariasis is markedly higher, being 13.3%[247] and 20.7%[74], respectively. In these regions, the infection occurs predominantly in adolescents and children.[52,247]

In male patients, scrotal dirofilariasis usually presents as painful swelling or nodule in the hemiscrotum, accompanied by erythema, sometimes with extension into the inguinal region, or even mild fever.[246,248–251] In rare cases, the nodules are painless, but gradually increase in size.[246,252] In exceptional cases, the infection can also manifest as an "acute scrotum" (a swollen erythematous hemiscrotum with oedema and pain)[253] or torsion of the testicle (significant, unilateral oedema of the scrotum with cyanotic tint of the affected area and tenderness).[184]

On the other hand, dirofilariasis of the spermatic cord, as the second commonest form, is often manifested by palpable painless, mobile and firm nodule of 2–4 cm in diameter.[254,255] In patients with associated acute inflammation, nodules are painful and may appear as abscesses. Also, inguinoscrotal, scrotal or testicular swelling, orchialgia and inguinal pain may be present.[188,246,256–258] In one unusual case, involvement of the spermatic cord caused significant symptoms that raised the suspicion of an incarcerated inguinal hernia.[255]

Epididymal dirofilariasis is generally characterised by the presence of a palpable, painless, soft or hard nodule in the epididymis of 1–2 cm in size.[187,244,245,259,260,261] On the other hand, swelling and intense pain in the scrotal region have been described in some cases,[18] even before the appearance of a nodule.[45]

Finally, dirofilariasis of the testicles and penis are very rare; each has been described in only three and six cases, respectively.[18,72,186,62,262,263] The testicular form of infection is manifested by testicular swelling and/or the presence of a tender nodule within

tissues of the testicle,[18,186] while patients with penile infection often complain of a painless, subcutaneous nodule on the ventral or dorsal surface of the penis.[62,262,263]

In males, genital dirofilariasis, which manifests as a nodular mass in the scrotum, is usually clinically indistinguishable from a benign or malignant neoplasm, particularly in the absence of systemic manifestation(s).[244] In clinical practice, the commonest testicular neoplasms are germ cell tumours, which account for >90% of cases.[264] Thus, any testicular mass should be considered malignant until proven otherwise.[265] On the other hand, differential diagnoses of symptomatic scrotal nodules caused by dirofilariasis may include epididymitis,[261] testicular tuberculosis, organised haematoma,[188] varicocele, spermatocele, hydrocele,[18,256] and some medical and surgical emergencies such as torsion of the testis,[184,250] acute scrotum[253] and incarcerated inguinal hernia.[255] Therefore, after excluding serious causes of these acute conditions, paediatricians and paediatric surgeons should consider dirofilariasis as a diagnosis.[253]

In female patients, dirofilariasis of the reproductive system is very rare, with only three cases reported to date. This disease manifested as cystic or tumorous masses in the ovary, fallopian tube and uterus.[183–185] Endometrial involvement may be accompanied by chronic uterine bleeding,[185] likely occurring as a result of inflammation. Immune and inflammatory processes in the female genital tract are under tight control and play a key role in facilitating the breakdown, regeneration and repair of the endometrium. During inflammation, increased leukocyte populations and elevated expression of pro-inflammatory mediators can contribute to hyperaemia, vasodilatation and coagulation disorders within the mucosa, potentially leading to menstrual disturbances and/or dysregulated bleeding patterns.[266] In women, genital dirofilariasis can clinically mimic a benign or malignant tumour.[183,185] The simultaneous presence of this form of dirofilariasis with a benign tumour in the same organ (e.g., Brenner tumour of the ovary) may be misinterpreted as a single mass with not entirely benign features.[183]

The occurrence of dirofilariasis manifesting as a nodular lesion in the female breast is also an uncommon event. According to the literature data, this infection has been caused predominantly by *D. repens*, although *D. immitis*, *D. tenuis* and *D. ursi*-like nematodes have also been reported in some cases, but the latter two species have been suggested without molecular verification.[22] Nodules have been recorded in both subcutaneous and glandular mammary tissues, with predilections to the upper outer quadrant of the left breast.[2,22,267–280] Recently, it was shown that, in some populations, the temperature of the upper left quadrant of the breast is higher than that of the right side, and that the upper quadrant is naturally warmer than the lower quadrant,[281] which may influence the attraction of mosquitoes and the pattern of mosquito bites.[282] In addition, as in the case of genital organs, the mammary gland represents the target for various hormonal stimuli emanating from the hypothalamic-pituitary axis, while steroid hormones dictate the concerted cyclical remodelling of this gland throughout a woman's life from menarche to menopause.[283] Therefore, a tropism of *Dirofilaria* species for higher hormone concentrations may explain occasional mammary gland infection. Dirofilariasis of the female breast usually manifests as a painful, intermittently painful or painless, mobile, firm and subcutaneous nodule of 1–4 cm (mostly ~1.5 cm) in size, which may be associated with erythema, pruritus and swelling of the overlaying skin. Nodules were first noticed by patients several weeks to six months (mostly two months) prior to clinical presentation.[22,267–280] In some cases, axillary lymphadenopathy[276,278,284] and fever have also been reported.[285]

In practice, mammary dirofilariasis may mimic an inflamed sebaceous cyst, fibroadenoma, fibrocystic disease or a pre-cancerous lesion.[267,270,274] Although rare, parasitic infection caused by *Brugia malayi*,[286] *Wuchereria bancrofti*; *Echinococcus granulosus*, *Taenia solium*, *Schistosoma* spp.; or *Sermatobia hominis* (human botfly), have also been recorded in breast tissues in different regions around the world.[284] Compared with tumours, breast lesions caused by dirofilariasis usually remain relatively consistent in size, and do not show alterations during the menstrual cycle, and there is no discharge from the nipples.[270] However, regardless of the benign features, breast lesions associated with dirofilariasis may also be initially misdiagnosed as carcinoma upon mammography, particularly when associated with micro-calcifications.[284] Therefore, clinical diagnosis demands a structured and comprehensive approach.

Pulmonary dirofilariasis

Human pulmonary dirofilariasis typically presents as a nodule ("coin lesion") in the lung parenchyma upon imaging and often raises concern of a malignancy.[287] Nodules are usually solitary, with well-defined margins and are 0.5–4.5 cm in size, spherical and usually non-calcified.[83,287–289] Although most lesions are smooth-bordered, they can be tufted or serpiginous in rare cases.[83,290]

It is important to emphasise that pulmonary dirofilariasis in humans is usually caused by *D. immitis* and rarely by *D. repens*.[291] Most of the cases caused by the latter parasite have been described by Italian research groups who also maintain international statistics on the incidence of human subcutaneous dirofilariasis caused by *D. repens*.[230,291–295] *D. repens* lung infection has also been recorded in several patients from Russia and individual cases from Greece,[296] France,[297] Slovakia,[298] Slovenia[299] and Egypt.[300]

"Coin lesions" appear to be more frequently located subpleurally (on the periphery of the lung parenchyma) than centrally, with a predilection to the right lower lobe of the lung, which may relate to the larger surface area of this lobe, more blood flow and/or an anatomical difference in the paths of pulmonary arteries. In contrast to the left pulmonary artery, which crosses over the left main bronchus, the right pulmonary artery runs straight through the anterior part of the right main bronchus.[85,301,302] Bilateral pulmonary lesions and multiple unilateral lesions are rare, but have also been recorded.[303–305]

Nodular pulmonary lesions can be classified morphologically as spherical ("coin lesions", the most commonly presented), wedge-shaped, pedunculated, pod-like, geographic, irregular or cavitated forms.[83,288,306–308] These lesions (nodules) can contain one immature, dead, degenerating or fragmented worm associated with a small pulmonary artery,[309] sometimes multiple worms have been found;[310–312] in patients with a compromised immune system (e.g., linked to acute lymphoblastic leukaemia), an encapsulated worm might be gravid.[20]

The pathogenesis of "coin lesions" likely relates to complete or partial occlusion of arterial blood vessels in lung parenchyma by the nematode(s) or worm fragments,[83] thrombus formation,[313,314] hypoxia,[83,315,316] necrosis and granuloma formation (including fibrosis).[83,290] Histopathologically, vascular alterations seen include endarteritis, periarteritis, intimal hyperplasia, fibroblastic proliferation and haemorrhage within the arterial wall, and perivascular inflammatory oedema and haemorrhage in the surrounding alveoli.[82] Sometimes, the elastic lamina of vessels can be partially or completely destroyed, occasionally resulting in extravasation,[302] nematode penetration into the bronchiolar lumen and granuloma formation.[313]

Clinically, pulmonary dirofilariasis is usually asymtomatic, although pulmonary or systemic manifestations can occur (chest pain, cough, fever, haemoptysis and/or dyspnoea) in some instances.[317] Pleural effusions, pleural infiltrates and pleural thickening have been reported in a minority of patients,[54,309] as have sporadic cases of partial atelectasis,[55] myocarditis, and dilated cardiomyopathy.[318] Interstitial oedema and pleural effusion can occur as a consequence of vascular inflammation. Vasculitis may be caused by the excretory/secretory molecules from a worm(s), and antigens from a dead or

dying worm might exacerbate immune responses.[82] Occasionally, serial chest X-rays can reveal the formation of a peripheral nodule in the region of previous pulmonary infiltrates. According to clinical studies, pneumonia-like infiltrates observed in human pulmonary dirofilariasis can evolve into nodules within three to 36 weeks.[304,319]

Nodules can be stable in size and configuration for periods of up to 4 years,[304] although there is some evidence of their potential for progressive enlargement,[320] spontaneous regression,[321] and of their transient nature.[322–324] In some cases, nodules can disappear over time following immune attack and subsequent tissue regeneration.[313] Calcification of nodules is rare and would need to be differentiated, clinically, from histoplasmosis, tuberculosis, hamartoma or a malignancy.[287,304]

Although pulmonary dirofilariasis is usually self-limiting, with no major health risk or known long-term complications,[309] differential diagnosis from other diseases, such as neoplasia, vascular disorders, infections and immunological diseases, is a challenge.[83] Cancers represent a leading cause of pulmonary nodules,[325] and the suspicion of malignancy is higher in smokers or patients with lung cancer-like symptoms.[289] In rare cases, elevated cancer markers and lung masses mimicking tumours with chest wall invasion have been reported in smokers with pulmonary dirofilariasis.[81,326] This evidence highlights that "watchful waiting" is an inappropriate approach for smokers.[325]

Similarly, an unusual case of human pulmonary dirofilariasis with an enlarging pulmonary nodule, following migrating infiltration shadows that mimicked primary lung carcinoma, was reported.[301] In this case, the worm migrated from the right upper lobe to the right middle lobe, where it initiated nodule formation.[301] However, in practice, the most complex cases are patients with previously diagnosed and treated malignancies, where pulmonary dirofilariasis can mimic a metastatic focus or tumour recurrence.[83,291,327–330] In some cases, the coexistence of pulmonary dirofilariasis with primary or metastatic lung tumours has been reported.[83,308,331,332] Thus, clinical suspicion of a mixed aetiology of pulmonary lesions should be raised based on radiologic characteristics and their divergent behaviour upon treatment – i.e. a malignant lesion might respond to chemotherapy and reduce in size, while a lesion induced by *Dirofilaria* would mostly remain unchanged.[308]

It should be emphasised that, in addition to *Dirofilaria*, other helminth species that might interact with the pulmonary microenvironment include *Ancylostoma duodenale*, *Anisakis* spp., *Ascaris lumbricoides*, *Brugia malayi*, *Echinococcus granulosus*, *Echinococcus multilocularis*, *Loa loa*, *Necator americanus*, *Ophidascaris robertsi*, *Paragonimus* sp., *Schistosoma* spp., *Strongyloides stercoralis*, *Toxocara canis, Toxocara cati* and *Wuchereria bancrofti*, [333–336] In nodules in which no worm is detected, the differential diagnosis may include thromboembolism with infarction, polyarteritis nodosa, Wegener's granulomatosis, eosinophilic pneumonia, histiocytosis X, hypersensitivity pneumonitis or common granulomatous conditions affecting the lungs, such as tuberculosis, histoplasmosis or coccidioidomycosis.[84] For instance, in a case with a solitary pulmonary lesion subsequently diagnosed as dirofilariasis, *Mycobacterium gordonae* was initially cultured from the sputum, but no bacteria were found in the lung biopsy specimen during further diagnostic workup.[337] This non-tuberculous mycobacterium, despite its avirulent nature, might be implicated, in rare cases, in the formation of pulmonary nodules,[338] representing a diagnostic challenge.

Cardiovascular dirofilariasis – a post mortem artifact of pulmonary dirofilariasis

There are five cases suggesting *D. immitis* infection involving the human heart or large vessels. In the first report, two nematodes, one of each sex, were recovered from the left ventricle of a boy from Brazil in 1887.[55] The second case was documented from New Orleans in 1941. In this case, a male worm was extracted from the inferior vena cava of a 73-year-old woman with acute toxic nephritis.[339] In the third case, reported in 1965, a 21 cm long non-gravid female parasite was found in the right heart of a 40-year-old, diabetic, female resident of New Orleans.[340] The fourth case of dirofilariasis affecting the human heart or large vessels was described in 1981 in a 36-year-old Japanese man with alcoholic hepatic cirrhosis. In this patient, two non-gravid adult female nematodes were recovered from the heart and inferior vena cava.[341] Finally, the fifth case of "cardiovascular dirofilariasis", reported in 1985, is remarkable for its localisation on a portacaval vascular prosthesis in a 32-year-old female patient from Jacksonville, Florida, USA. This patient had a long history of alcoholism and hepatic cirrhosis, a mature, but nongravid, female nematode was found to be coiled within the portacaval shunt and protruding into the inferior vena cava.[342]

It is important to emphasise here that all five cases were documented at autopsy, and that there was no unequivocal evidence that the parasites were linked to disease and a fatal outcome. Indeed, the presence of *Dirofilaria* worms in the heart and inferior vena cava might represent a post-mortem artefact, as they have not yet been detected by any imaging technique within these organs in the live human organism.[82]

Allergy

There is some evidence that different types of human filariasis, particularly "heartworm", may cause allergic reactions in humans.[343,344] It has been shown that the contact with *D. immitis* can contribute to the development of allergic reactions in atopic individuals in endemic areas.[345] In addition, a relatively high prevalence of allergy was observed in dog owners living with their infected pets, and it was hypothesised that constant contact with infected vectors in hyperendemic regions might induce specific IgE responses against *D. immitis*, contributing to the development of hypersensitivity. Likewise, in a serological study, conducted on human population from areas where canine heartworm is more widespread, a relationship between seropositivity to anti-*D. immitis* and anti-*Wolbachia* surface protein (WSP) IgG antibody levels was established, and high IgE levels were detected in the sera of subjects examined. Furthermore, the presence of anti-*D. immitis* IgE was demonstrated in persons who were also seropositive for anti-*D. immitis* IgG antibodies. Previously, it has been shown that *D. immitis* infection can cause bronchoconstriction and bronchospasm in non-permissive animal hosts, such as cats.[344]

In addition, there is evidence that *Dirofilaria* infections of the subcutaneous tissue can induce acute or chronic urticaria (*D. repens*), or anaphylaxis (e.g., "Hong Kong" genotype of *Dirofilaria*).[191,192,63,346] Based on the literature, acute urticaria has so far been described in two patients with subcutaneous dirofilariasis. Interestingly, both patients developed urticarial lesions on the skin of the upper extremity, but a standard haematological examination showed pronounced eosinophilia in only one of them.[191,346] In the literature, a case of chronic, apparently idiopathic urticaria, resulting from a subcutaneous *Dirofilaria* infestation in the right axillary region, was recorded.[192] Upon admission, the patient had massive urticaria with intense itching resistant to conventional antihistamine therapy and was only partially and temporarily responsive to corticosteroid therapy.[192] Finally, anaphylaxis, as an acute, potentially fatal, systemic allergic reaction with different mechanisms and clinical presentations,[347] has also been reported in an exceptional human case with subcutaneous dirofilariasis located on the forearm.[63] In this patient, partial damage to the nodule during surgery likely led to the sudden release of antigenic components from the worm, triggering an anaphylactic reaction. This case, apart from its uniqueness, is worth mentioning because it indicates the importance of complete "en bloc" excision of suspected dirofilarial lesions, in order to

prevent potential anaphylaxis, particularly in patients with atopic constitution, and when surgeons encounter dense adhesions or multiple blood vessels supplying the lesions.[63]

Diagnosis

Central to the diagnosis of human dirofilariasis is the physician's suspicion that the parasite could be the underlying cause that led to the formation of the nodule discovered in the patient. However, this possibility is too often overlooked in clinical practice. Such awareness requires an understanding of the biology of the parasite, as well as insight into its distribution and occurrence in humans. Therefore, a thorough diagnostic protocol should include obtaining a sound anamnesis; consideration of factors such as background of the patient; possible contact with vectors and other biological, racial and ethnic factors, as well as lifestyle and behavourial aspects; and clinical diagnosis should be supported through the use of complementary imaging and laboratory tools.

Anamnesis and aspects to consider when making a diagnosis

History

Most of the information aiding an accurate diagnosis in clinical practice is from attentive listening to the patient's history. In many patients, human dirofilariasis is asymptomatic or accompanied by mild symptoms and, therefore, might go unrecognised.[30,49,348] In unusual cases of human dirofilariasis, other specific symptoms (mentioned in the previous section) may also occur. Finally, knowledge that a patient with a subcutaneous or ocular inflammatory lesion has been unsuccessfully treated previously with antibiotic and/or corticosteroid therapy is of great diagnostic importance.

Contact with vectors

A recent mosquito bite may represent one of the clinical clues for suspected dirofilariasis, though many patients may not recall having been bitten, as mosquito or insect bites often go unnoticed, unless a visible skin reaction occurs. Outdoor activities, particular occupations and outdoor recreation can increase exposure to mosquito bites, emphasising the importance of a detailed history of lifestyle and activities.[349,350] In some cases, bites may go unnoticed if the site is not readily visible, such as on the back.

Socio-epidemiological anamnestic data that may raise a clinical suspicion of dirofilariasis

During the diagnostic process, it is important to establish patient's place of residence, travel history, profession and cultural and behavioural habits. The information that a patient lives in, or has travelled to, a "mosquito-infested" area which is (potentially) endemic for *Dirofilaria* is important and raises a clinical suspicion of this disease.[164] Likewise, in patients who own a dog, it is useful to obtain information regarding the origin of the dog and its travel history, as well as prior preventive treatment against canine dirofilariasis. On the other hand, for pet owners with a high clinical suspicion of dirofilariasis, who have a dog on a preventative treatment regimen, contact with mosquitoes that have taken blood meal from potentially infected domestic or wild canids in a surrounding neighbourhood should be considered, as well as resistance of the parasite to macrocyclic lactones (e.g., ivermectin) – reported in domestic animals.[32,42,351]

In addition to detailed history-taking and a suspicion about infection (Box 1), non-invasive imaging techniques and targeted laboratory examinations are useful tools for establishing a differential and definitive diagnosis of *Dirofilaria* infection in an individual patient.[13,34]

Diagnostic imaging tools

Ultrasonography

Sonography is usually not performed on patients with subcutaneous nodules prior to surgical excision, unless such lesions are near lymph nodes or large blood vessels.[35] However, this imaging method, combined with colour and power Doppler techniques, can be useful to indicate that nodules are of parasite origin, regardless of their location (superficial or deep). Diagnosis relies on morphological features of the nodules, the presence of worm-like structures resembling parallel hyperechoic lines within the nodules, and the observation of worm movements in live worms during mechanical stimulation – "filarial dance sign",[247,259,352,353] originally documented by Brazilian radiologist Fernando Amaral and his team in a cohort of 14 individuals with *Wuchereria bancrofti* infection in 1994.[354] Regardless of a lack of movement, a diagnosis can be established by echosonography if the structure of the parasite is preserved, and differentiation from cancerous lesions, benign neoplasms, cystic lesions, abscess or different systemic granulomatous diseases is critical. The peripheral location of blood vessels in *Dirofilaria* nodules, as opposed to the vascularisation within the nodules seen in malignant tumours, can further support the diagnosis.[247,353] Also ultrasound can facilitate and guide invasive procedures, such as fine needle aspiration (FNA) biopsy, performed in patients with clinically suspicious soft-tissue masses, particularly those located in female breasts. Therefore, sonography, as a safe, inexpensive, real-time portable method,[355] should be included as an important tool for the differential diagnosis of subcutaneous nodules, especially in cases where a parasitosis is suspected.

X-ray, computed tomography, magnetic resonance imaging and positron emission tomography

Other radiographic imaging techniques primarily serve to guide the diagnosis of pulmonary dirofilariasis. This approach allows the identification of "coin lesions" via chest X-rays, which might lead to the characterisation of the worm-like structures in the lesions by computed tomography (CT) or magnetic resonance imaging (MRI). Although CT findings are not specific for pulmonary dirofilariasis and may, in some cases, suggest an abscess (heterogeneous mass of soft tissue with peripheral enhancement), this imaging modality might facilitate the differentiation of a benign pathologic entity from a malignant tumour.[353,356,357] If performed by an experienced professional, CT-guided percutaneous fine needle aspiration biopsy (FNAB) of pulmonary "coin lesions" might be able to exclude the possibility of a malignancy following cytological analysis of the biopsy specimen.[358–360] In recent years, examination of incidental pulmonary nodules has rapidly emerged as the primary indication for 18-fluorodeoxyglucose (FDG) positron emission tomography (PET). FDG PET identifies malignancy by detecting elevated FDG uptake, which indicates increased glucose metabolic activity in cancer cells.[361] Interestingly, it has been shown that pulmonary nodules of dirofilarial origin may occasionally exhibit increased metabolic activity on PET scan, complicating the pre-surgical differentiation between human pulmonary dirofilariasis and a malignancy.[287,289,362,363] Currently, this technique is combined with CT (PET-CT), which reduces the likelihood of a misdiagnosis.

On the other hand, in patients with subcutaneous dirofilariasis, three-dimensional (3D) imaging techniques can be used to evaluate the morphology of nodules in deep soft tissues (muscles), visceral organs or difficult-to-reach areas, such as body cavities (especially orbit). In regions where subcutaneous dirofilariasis is prevalent, 3D-imaging techniques have demonstrated their utility in distinguishing nematode-induced granulomata from tumours.[364] Upon MRI, the worm exhibits hypo-intensity in both T1- and T2-weighted images, with the potential for irregularly bordered hyperintensity in T2 or STIR images. Post-contrast enhancement is typically ill-defined and

Box 1
Anamnestic data or information important for raising clinical suspicion of dirofilariasis in a patient.

(1) A patient who complains of the presence of a solitary, inflammatory/non-inflammatory subcutaneous lesion of unknown origin.
(2) A patient who had a negative chest X-ray about a year ago and has developed "de novo" solitary pulmonary nodule, which is either asymptomatic or associated with mild respiratory symptoms and located in any lobe of the lungs.
(3) The presence of a single, rarely multiple, subcutaneous migratory local swelling or nodule.
(4) History of mosquito bite in recent weeks or months preceding the onset of symptoms.
(5) An unsuccessful treatment of subcutaneous or ocular inflammatory lesions with an antibiotic and/or corticosteroid.
(6) Sensation of movement ('crawling') under the skin.
(7) The presence of cutaneous larva migrans symptoms (a small reddish papule that progresses to a serpiginous pruritic rash).
(8) Residence, business/recreational activities or holiday trips to endemic zones, areas near surface water (ponds, swamps, rivers, canals, reservoirs and/or lakes) and/or overgrown with lush vegetation, or in regions with a warmer climate and increased relative humidity - "mosquito-infested areas".
(9) Outdoor activities on irrigated and flooded fields (farmers).
(10) Travel history of dogs and their owners to endemic areas.
(11) Contact with dogs imported/rehomed from endemic areas that have not undergone adequate veterinary checks or care.
(12) Contact with dogs from a neighbourhood that have not received any prophylactic treatment (e.g., animal shelter).
(13) Contact with known microfilaraemic dogs.
(14) An outdoor lifestyle accompanied by a high rate of exposure to bites from mosquitoes associated with wild dogs and/or other carnivores as potential reservoirs of infection (e.g. farmers, fishermen, hunters, gamekeepers, forest guards, wild plant gatherers, soldiers, adventurers, athletes, etc.).

likely attributed to the surrounding inflammation.[212,353] In patients with central nervous system complications secondary to subcutaneous dirofilariasis, MRI findings might exclude other causes, such as acute ischaemia, haemorrhage or venous occlusions.[48] However, the spatial resolution of MRI is sub-optimal for a direct assessment of a worm due to the small size of the latter. MRI lacks specificity, such that worm nodules may mimic other lesions including sebaceous cysts or small abscesses.[353]

Laboratory-based diagnosis

To date, the definitive diagnosis of dirofilariasis is mainly based on histopathological findings. Due to the lack of a specific clinical manifestation, most physicians are unlikely to suspect the parasitic nature of a nodule prior to a biopsy, except when the parasite is visible (subconjunctival dirofilariasis).[365] Furthermore, despite advances in our knowledge of *Dirofilaria* nematodes and the pathologies that they cause in different hosts in the veterinary field,[2] many (human) medical clinicians are unfamiliar with this parasitosis. The path to a definitive diagnosis of human dirofilariasis is shown in Fig. 3.

Serological and immunological methods

Serological tests, such as the enzyme-linked immunosorbent assay (ELISA), complement fixation, immunofluorescent antibody and indirect hemagglutination tests, have been developed for filarial nematodes, but are not widely available and sufficiently specific or sensitive for the definitive diagnosis of human dirofilariasis.[54,319] As most *Dirofilaria* species do not develop well in the human host, infections are usually not patent (i.e. microfilariae are not present or detected in the blood stream), and anti-filarial serum antibody levels are low or undetectable. Nonetheless, in patients with a travel history to, but no residence in endemic areas, the presence of serum antibodies against filarial worms can suggest the possibility of infection, although serological cross reactivity among nematode species is common.[7] In addition, serological procedures may assist in the diagnostic process, but in patients with suspected pulmonary dirofilariasis (e.g., *D. immits*), pulmonary neoplasm cannot be excluded using serology alone.[366]

Currently, ELISAs using antigens, such as Di22, a 22 kDa polypeptide antigen (derived from *D. immitis* somatic antigens)[367] or recombinant fusion protein,[368] are available and seem relatively specific (90% and 100%) and sensitive (100% and 100%), but their use is limited.[54] However, most different somatic and purified antigens employed in the past have led to high cross-reactivity (≤30%).[54] Interestingly, the recent validation of a non-commercial ELISA for the detection of *D. repens* antibodies, based on a unique purified somatic antigen of immature female worms removed from human cases and developed by Russian scientists, showed a sensitivity of 75.4% and a specificity of 88.9% for the diagnosis of cases in which parasites were migrating through subcutaneous tissues.[369] It seems also that a Western blot approach achieved promising results for the detection of specific antibodies against *D. repens*, but further work is necessary before a conclusion can be made about its performance for diagnosis in humans.[187]

Given the challenges with serological/immunological techniques, it is important to emphasise that they should be used exclusively as a complementary tools to assist in the diagnosis of human dirofilariasis, supported by additional information, such as medical history, region of residence and radiography, and a careful interpretation of all findings in the clinical context of each patient, before resorting to an invasive diagnostic procedure.[2]

Eosinophils and serum IgE

Peripheral eosinophilia and/or elevated serum IgE levels are rarely observed in patients with dirofilariasis. Based on the literature, eosinophilia has been reported in up to 20% of patients with pulmonary dirofilariasis, and may support a diagnosis in conjunction with the detection of coin lesions upon radiological examination.[102] On the other hand, with the exception of one study that showed blood eosinophilia in 38% of patients,[369] this is rarely observed in patients with subcutaneous infection.[370] IgE are not routinely measured and may be a useful parameter in suspected dirofilariasis provided a patient does not have an allergy.[187]

Detection of circulating larvae

The modified Knott's test is used routinely to detect and identify microfilariae in the peripheral blood of humans and animals.[371] This test is practical, rapid and inexpensive to perform, and can be used in a qualitative or quantitive manner.[372,373] Also, it represents a cost-effective diagnostic test for *D. repens* infection in veterinary medicine, for which, contrary to *D. immitis* infection, no rapid, easy-to-perform in-clinic test kits and specific serological tests are available.[7,373] However, obviously, it cannot detect prepatent or occult (amicrofilaremic) infection.[374] The technique involves diluting 1 mL of EDTA venous blood with 9 mL of 2% formalin containing formaldehyde (which is mutagenic and genotoxic).[375] A recent study suggests that distilled water can be used instead of formalin for the

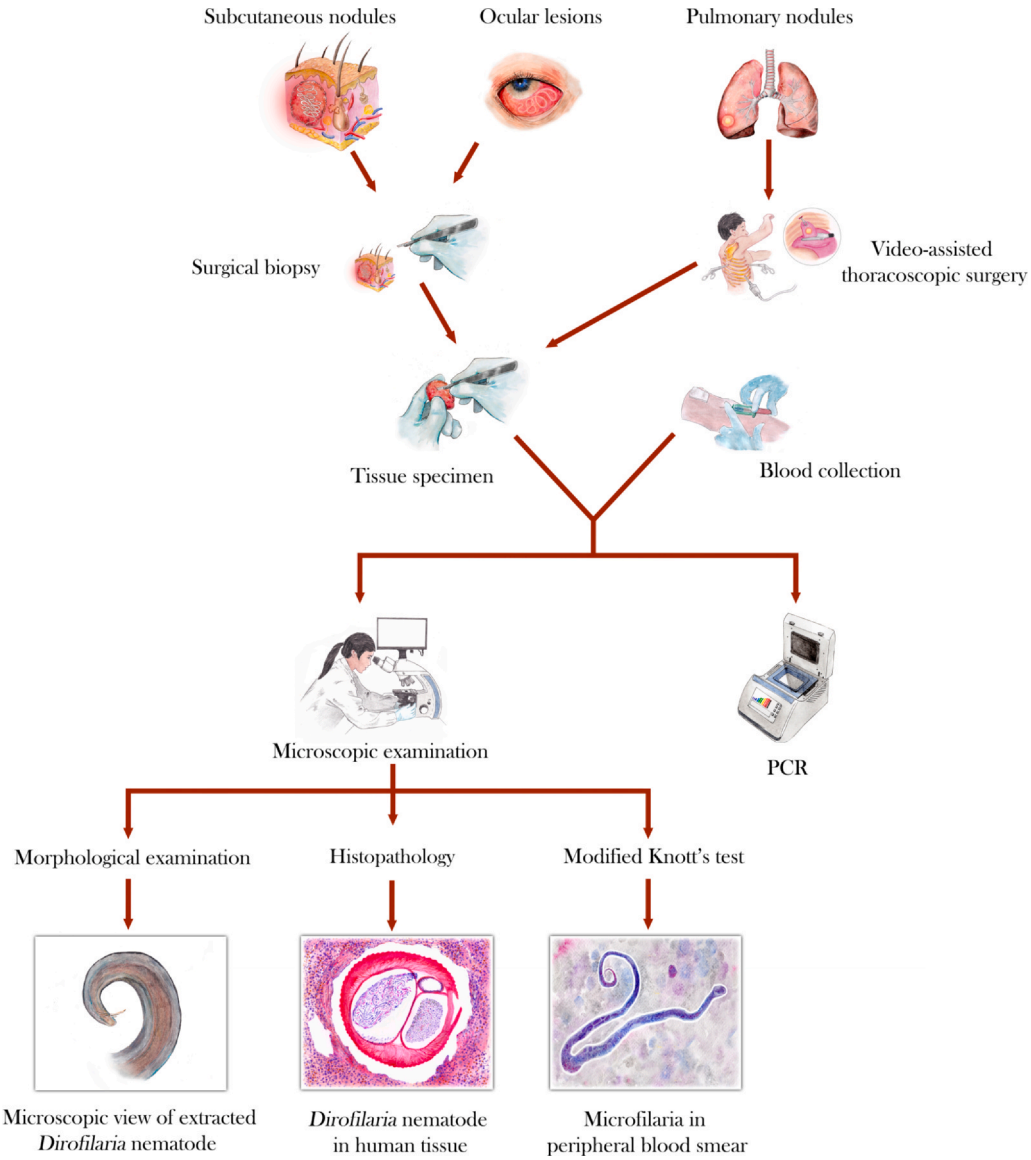


Fig. 3. Flowchart for making a definitive diagnosis of human dirofilariasis.

detection of *Dirofilaria* spp.[376] Nevertheless, modified Knott's accurate identification and differentiation of various species based on the morphology and morphomterics of microfilariae is challenging due to their similarity, and microfilaremic infections are simply not detected. In these situations, the use of molecular and specific staining methods might be used to complement the Knott's test.[14,373,377] Finally, the Knott test is of little practical interest in human infections due to the unusual presence of circulating microfilariae.

Histopathological examination

Following the surgical removal of a nodular lesion, the material is usually submitted for macroscopic and microscopic examination by a trained pathologist. It is important to emphasise that the histopathological characteristics of nodules are influenced by the duration of the parasite's presence in tissues and the host's inflammatory response.[378] The preparation of high-quality histopathological sections is critical.

In patients with pulmonary dirofilariasis, macroscopically, a lesion appears as a well-circumscribed, rounded nodule with a grey fibrous periphery and a granular light grey to tan centre.[293,306] Microscopic analysis of surgically resected nodules reveals central coagulation and necrosis of the lung parenchyma involved, usually surrounded by a granulomatous zone consisting of epithelial cells, plasma cells, lymphocytes and, occasionally, giant cells. Towards the periphery, the lesion is demarcated by fibrous tissue, and the lung tissue contains scattered gatherings of lymphocytes, macrophages, some giant cells and eosinophils.[180,359] The pulmonary vessels, whether near the nematode or not, may exhibit varying levels of endarteritis.[293] Worms can be found by conducting a thorough examination of serial histological sections, as they are typically located within the central necrotic tissue, often inside a lumen of arterial vessel. They can be recognised, without special stains, as large, round or oval formations with an average cross-sectional diameter of 200 µm (100–350 µm). Worms can be identified based on their thick, multi-layered cuticle (ranging from 5 to 25 µm) with fine transverse striations, prominent internal longitudinal cuticular ridges (although they may not always be visible in tissue sections), internal organs such as bands of somatic muscle extending into the body cavity, and reproductive tissues (https://www.cdc.gov/dpdx/dirofilariasis/index.html).[319]

On the other hand, in patients with subcutaneous dirofilariasis – mostly caused by *D. repens* – the microscopic examination of histological sections reveals a pseudocystic cavity surrounded by a fibrous capsule with intense inflammatory cell infiltrate(s) composed of eosinophilic granulocytes, histiocytes, plasma cells and

lymphocytes. This cavity contains sections of the nematode (220–660 µm in diameter), characterised by a thick multilayered cuticle (5–20 µm) with longitudinal, regularly dispersed ridges on the circumference that have a height of 2–6 µm and are separated by an average distance of 12 µm, which is a characteristic feature for diagnosis. In the lateral cord area, the worm's cuticle shows a triangular internal bulge. Mostly, a female worm is found, with a double uterus (usually without microfilariae), an alimentary tract and musculature of coelomyarian type. In contrast, the male worm possesses a single reproductive tube.[7,15,212,246] The diagnostic features of *D. tenuis* resemble those of other *Dirofilaria* species, particularly *D. repens*. In cross-section, *D. tenuis* has longitudinal ridges, and its diameter ranges from 280–330 µm. However, the latter species exhibits ridge characteristics that are distinct from other dirofilariae found in humans; its ridges are relatively low and rounded, with a wavy, broken and branched pattern and an inter-ridge spacing that is narrower than the ridges themselves (https://www.cdc.gov/dpdx/dirofilariasis/index.html).[379]

Morphological examination of the worm

If a live, adult worm can be extracted from a nodule, a morphological and morphometric examination is usually performed by an expert parasitologist. Macroscopically, the cuticle of *D. repens* specimen is whitish and has noticeable longitudinal ridges on its surface. The cuticle narrows at the ends. Males range in length from 48 to 70 mm and in width from 3.7 to 4.5 mm. On the other hand, females are larger, measuring 100 to 170 mm in length and 4.6 to 6.5 mm in width. For detailed microscopic examination, lactophenol or glycerine is used to prepare temporary mounts for the identification of specific morphological features. In females, the vagina opens at a distance of 1.1 to 1.9 mm from the oral aperture. In males, two spicules of 430 to 590 µm and 175 to 210 µm, respectively, can be seen and measured. In addition, 4 to 6 precloacal papillae (1 to 2 post-anal and 3 caudal papillae) are characteristic.[7]

Adult *D. immitis* worms have a thin, thread-like shape (hence, "filiform"). Females are 250–300 mm in length and 1 to 1.3 mm in diameter, whereas males are 120 to 200 mm in length and 0.7 to 0.9 mm in diameter. The lack of longitudinal cuticular striations in *D. immitis*[2,380] is a key morphological feature to distinguish it from *D. repens*.

For *D. tenuis*, adult females are typically 80 to 130 mm in length and 260 to 360 µm in width, whereas adult males are usually 40 to 50 mm long and 190 to 260 µm wide. On the surface of the cuticle, except at the ends, there are longitudinal ridges that give it the appearance of beads, which can be readily seen macroscopically and in microscopic sections. The most significant morphological features are seen in cross-sections of the worm: the cuticle consists of multiple layers and is ~5 to 8 µm thick in live worms. The longitudinal ridges are low and smoothly rounded, with a distance of ~10 µm between ridges. In the midbody region, ~90 ridges can be counted. On the inner surface of the cuticle in the lateral fields, there is a prominent ridge that extends into the inner surface of the lateral chords.[381]

Molecular diagnosis

Employing informative genetic markers, polymerase chain reaction (PCR)-based sequencing can achieve specific amplification of DNA from *Dirofilaria* nodules and can provide an unequivocal diagnosis, even when a tiny amount of degraded worm is obtained upon surgical biopsy. This approach performs best if parasite material processed directly or following freezing, but ethanol fixation, followed by cooling or freezing is also possible for sample storage. It is important to emphasise that the parasite material should not be fixed in formalin; unfortunately, this occurs frequently in clinical practice. PCR is also applicable to blood samples, allowing the specific identification of microfilarial DNA and *Wolbachia*, which may prove beneficial in recognising a recent *Dirofilaria* infection.[2,12,54,128,382]

PCR-based sequencing of *Dirofilaria* can have major advantages over conventional methods in that they are inexpensive and rapid to perform and can achieve an unequivocal diagnosis and allows the genetic characterisation of individual worms (larvae or adults) from nodules or lesions. In a clinical context, being able to make a specific diagnosis and exclude a cancer as a cause of a nodule, this method can lead to major benefits, such as a substantial acceleration in the management of dirofilariasis and the elimination of additional costs associated with pursuing a cancer diagnosis (with or without exploratory surgery).[54] In addition, the genetic characterisation of worms contributes to understanding the genetic make up of *Dirofilaria* populations in different areas and host species (mammalian and arthropod) and their relationships,[383] genetic diversity within and among species and genotypes (e.g., "Hong Kong") of *Dirofilaria*. Investigations employing mitochondrial and nuclear gene markers will also aid in identifying the origins of isolates in new endemic regions and tracking the spread of the infection. In the future, genome-wide analyses should reveal the presence of subpopulations or cryptic species that may differ in biological aspects, including zoonotic potential, vector preference, host resistance and transmission patterns.[230]

Treatment and management

Surgery

In most human clinical cases, simple extraction of the worm or complete surgical excision of a nodule is both a diagnostic and treatment modality for human dirofilariasis. However, it is important to emphasise that, in some cases, ocular and subcutaneous dirofilariasis cases, routine surgery may be ineffective due to active parasitic migration, and can result in complications. Actually, the migration of a worm is unpredictable, and a delay in surgical intervention, whether due to scheduling or a referral, poses a risk to the limited time frame available to reliably extract the worm.[384] As migrating worms can cause significant damage to sensitive structures, such as in the eye, they should be removed promptly.[125] Furthermore, in patients with intraocular infection, intact deworming is imperative, because the dead worm can also induce endophthalmitis linked to the bacterial endosymbionts (*Wolbachia*) from the nematodes.[130] In such situations, migratory worms should be immobilised (if possible) and removed in their entirety. For periocular locations, visible worms should be directly removed by establishing a pharmacological barrier around the worm using 1% lidocaine with 1:100,000 epinephrine; this prevents the worms from "retreating" into deeper, inaccessible structures within the eye. Once the escape routes are effectively sealed, additional anaesthetic is injected near a worm to immobilise it, facilitating effective removal.[384] In addition, Gendelman et al.[385] described the use of a cryoprobe as another possible approach to immobilise subconjunctival worms.

For the management of intraocular infections, other approaches have been documented. For instance, photocoagulation appears to be useful and has been suggested to kill the parasites. However, when the parasite is located in the posterior pole of the retina, photocoagulation can lead to permanent visual impairment, requiring subsequent surgical removal. In some cases, worms have been removed from preretinal or subretinal locations by pars plana vitrectomy.[125] Recently, a new method for the surgical removal of a (complete) worm from the vitreal cavity using a closed manual aspiration system via 2-port access 25 G (without vitrectomy) was developed.[25] This approach is minimally invasive and does not affect the integrity of the nematode, providing favourable conditions for the specific identification of the worm (by conventional and molecular means) and for a patient rehabilitation.[25]

For subcutaneous dirofilariasis, treatment with anthelmintic drugs (including albendazole, diethylcarbamazine and/or ivermectin; see

next section) and doxycycline can reduce or stop the migration of the worm and can promote nodule formation.[102] Consequently, anthelmintic treatment should be applied as analternative to surgical intervention during the phase of parasite migration in order to prevent potential complications such as, for example, facial nerve injury.[369]

For pulmonary dirofilariasis, lung operations have not resulted in significant complications, with the exception of one case with dense pleural adhesions linked to post-operative bleeding.[289] Video-assisted thoracoscopic surgery (VATS), which involves minimal resection of the lung parenchyma, is less invasive compared with open surgery and associated with fewer post-operative complications, less pain, better post-operative quality of life, and similar outcomes.[386] Therefore, currently, it is the best option for the diagnosis and treatment of pulmonary dirofilariasis.[55,387]

Chemotherapy

Currently, there are no established protocols on the use of antiparasitic drugs for the treatment of dirofilariasis in humans, leaving physicians to depend on their own experiences and expertise.

Albendazole, methyl (5-(propylthio)-1H-benzimidazol-2-yl] carbamate) and mebendazole (methyl 5-benzoyl-1H-benzimidazol-2-yl-carbamate) are known to inhibit microtubule functions in both parasites and mammalian cells by preventing polymerisation of ß-tubulin into microtubules. This inhibition interferes with glucose uptake and transport, ultimately leading to glycogen depletion in the parasite. When used at recommended doses for short durations (1–3 days), albendazole and mebendazole are considered safe, with minimal side effects. However, they are not very bioavailable, and prolonged use for treating tissue or intestinal helminthiases or cancers can lead to liver toxicity, allergic reactions and, rarely, myelosuppression, particularly neutropenia.[388]

Diethylcarbamazine (N, N-diethyl-4-methyl-1-piperazine carboxamide, DEC) is an anti-filarial drug. The drug exhibits cytotoxic effects on microfilariae shortly after administration (~6 mg/kg of body weight), and it is only active at the moulting stages, although the precise mechanism of action is unknown. Nonetheless, DEC is known to interfere with arachidonic acid metabolism by inhibiting prostaglandin H synthase (PGHS, or cyclooxygenase), making worms more susceptible to immune attack.[389,390] On the other hand, recent research has indicated that DEC has the ability to activate transient receptor potential (TRP) channels, including TRPC ortholog TRP-2 and transient receptor potential channel, M subtype (TRPM) orthologs GON-2 and CED-11, in the nematode.[391]

During the treatment of patients with filarial infections, DEC has been shown to cause adverse reactions, particularly during the first 1–2 days of administration. These reactions include allergic responses, such as high fever, lymph node swelling, fatigue, and others, as well as toxic reactions including dizziness, drowsiness, headache, lumbago, loss of appetite, nausea and abdominal pain. These side effects are dose-dependent and closely related to the density of microfilariae in the blood,[392,393] as seen for the treatment of dogs with patent *D. immitis* infection.[24] Elevated fever is typically accompanied by leukocytosis.[392,393] As DEC is a prophylactic drug to prevent infection, has to be administered daily (to be effective) and is only active when larvae moult from L3 to L4, and, should thus not be used in patients with microfilaraemic dirofilariasis.[394]

Ivermectin (IVM), one of the best-known and widely used antiparasitic drugs, is a macrocyclic lactone that exhibits broad-spectrum activity against filarial parasites. Despite the well-established efficacy of IVM in treating various parasitic infections, its precise mechanism of action is not yet fully understood. IVM affects nematode motility, feeding, and reproduction (inhibits production of microfilariae *in utero*) at nanomolar concentrations, primarily acting through ligand-gated chloride channels, particularly those gated by glutamate. These glutamate-gated chloride channels (GluCls) are absent from vertebrate cells, contributing to the broad safety margin of IVM. However, at micromolar concentrations, IVM can interact with a broader spectrum of ligand-gated channels found in both invertebrates and vertebrates, encompassing GABA, glycine, histamine, and nicotinic acetylcholine receptors.[395] In individuals with high microfilarial densities in blood or tissues, IVM can cause a complex inflammatory reaction known as Mazzotti reaction due to massive drug-induced microfilarial destruction, characterised by pruritus, rash, fever, malaise, lymphadenopathy, arthralgia, tachycardia, hypotension, oedema and abdominal pain.[10,396] A recent study identified ten dirofilariasis cases from the literature that also linked ivermectin to skin reactions, nephropathy, psychiatric disorders, liver disorders and multiorgan dysfunction syndrome.[396]

On the other hand, ivermectin appears to have a limited ability to penetrate the blood-brain barrier in humans because it is actively excluded by the P-glycoprotein (mdr-1) drug pump. Consequently, it is considered unlikely to cause neurological adverse drug reactions, except when overdosed. However, a recent study revealed adverse neurological events, such as tremor, inability to walk, impairment or loss of consciousness, seizures, convulsions, encephalopathy and coma following administration of doses ranged between 3 and 24 mg/day (< 0.4 mg/kg body weight;[397] usual dosage of IVM in practice 0.15–0.2 mg/kg, approved in doses of up to 0.4 mg/kg).[398] Given the rarity of microfilaremia caused by *D. repens* in humans, the use of IVM is not firmly established in the literature, and there is only a limited number of case reports to date. For microfilaraemic dirofilariasis, where IVM is either contraindicated or refused by the patient, alternative drugs, particularly doxycycline, might be considered as an off-label treatment option.[10]

Doxycycline, an antibiotic belonging to the class of the tetracyclines, interferes with protein synthesis in bacteria by binding to the 30S subunit of the ribosome. In addition to the usual antibacterial applications, doxycycline is also prescribed to combat some parasitic diseases.[399] By targeting *Wolbachia* in some *Dirofilaria* and other filarial species,[400] this antibiotic agent results in sterility, elimination of microfilariae and gradual death of adult filariae.[401] Doxycycline is well-tolerated, compared with related tetracyclines, with limited evidence of causing serious side effects (which might include headache, dizziness, nausea, gastrointestinal upset, photosensitivity skin and tooth discoloration and rash for tetracyclines).[402]

Very rarely, in patients with *D. repens* microfilaremia, surgical removal of subcutaneous lesions is not sufficient to eliminate microfilariae from the peripheral blood, and requires the complementary administration of anti-filarial drugs.[377] Also, the use of such drugs may be justified in immunocompromised patients,[7] if secondary lesions are suspected in deep areas of the body such as the chest or abdomen to prevent invasive surgery, or after heavy exposure to mosquitoes in an area known to be endemic for dirofilariasis.[163] In some patients with subcutaneous dirofilariasis (as mentioned above), surgery is not feasible due to the active migration of parasites in tissues, and, therefore, chemotherapy, including a combination of albendazole (800 mg per day for 5 days) and doxycycline (200 mg per day for 5 days), has been shown to result in a positive outcome.[388]

The adverse effects of antifilarial drugs, although rarely fatal, can be severe enough to deter individuals from initiating or completing treatment. Therefore, when this treatment is indicated, a patient should be thoroughly informed about the potential harm and benefits of chemotherapy.[403]

Concluding remarks

For physicians and surgeons, nodular lesions in tissues continue to represent a major diagnostic challenge in clinical practice. Sometimes the appearance of nodules can be a first sign of an underlying disease, but due to the different manifestations and the

wide range of possible, associated pathological entities, the clinical evaluation of patients with nodules is far from simple, even for very experienced specialists. Given that, in most medical courses at universities around the world, Parasitology usually forms only a very minor component of an infectious disease curriculum, if at all, clinicians may not suspect the involvement of parasites in causing nodules.

This review elevates awareness of dirofilariasis as a zoonosis, particularly given the expected impact of global warming, human and animal migration, and changes in vector population ecology on its occurrence and prevalence in areas previously considered to be free from *Dirofilaria*, such as in northern Europe. In addition, continuing education in this field and improving the cooperation of clinicians and surgeons with veterinarians, medical entomologists and public health experts within the context of a One Health paradigm are highly recommended. This approach can also assist radiologists and diagnosticians in selecting appropriate imaging techniques to prevent misdiagnoses, leading to a reduced use of unnecessary medications, shortened diagnostic timelines, and improved patient satisfaction and outcomes.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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