Carney complex: Clinical and genetic 2010 update

Le complexe de Carney en 2010

D. Vezzosi\textsuperscript{a, b, 1}, O. Vignaux\textsuperscript{b, c}, N. Dupin\textsuperscript{b, d}, J. Bertherat\textsuperscript{a, b, e, *}

\textsuperscript{a} Inserm U1016, CNRS UMR 8104, institut Cochin, 24, rue du Faubourg-Saint-Jacques, 75014 Paris, France
\textsuperscript{b} Université René-Descartes, France
\textsuperscript{c} Department of Radiology A, hôpital Cochin, 24, rue du Faubourg-Saint-Jacques, 75014 Paris, France
\textsuperscript{d} Department of Dermatology, hôpital Cochin, 24, rue du Faubourg-Saint-Jacques, 75014 Paris, France
\textsuperscript{e} Department of Endocrinology, service des maladies endocriniennes et métaboliques, National Reference Center for Rare Adrenal Disorders, hôpital Cochin, 27, rue du Faubourg-Saint-Jacques, 75014 Paris, France

Available online 17 September 2010

Abstract

First described in the mid 1980s, Carney complex is a rare dominantly heritable multiple endocrine neoplasia syndrome that affects endocrine glands as the adrenal cortex, the pituitary and the thyroid. It is associated with many other nonendocrine tumors, including cardiac myxomas, testicular tumors, melanotic schwannomas, breast myxomatosis, and abnormal pigmentation or myxomas of the skin. The Carney complex gene 1 was identified 10 years ago as the regulatory subunit 1A of protein kinase A (\textit{PRKAR1A}) located at 17q22-24. An inactivating heterozygous germ line mutation of \textit{PRKAR1A} is observed in about two-thirds of Carney complex patients. This last decade many progresses have been done in the knowledge of this rare disease and its genetics. This review outlines the current state of this knowledge on Carney complex.

© 2010 Elsevier Masson SAS. All rights reserved.

Keywords: Carney complex; \textit{PRKAR1A} gene mutation; Primary pigmented nodular adrenocortical disease; Cardiac myxoma; Cutaneous lentiginosis

1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNC</td>
<td>Carney complex</td>
</tr>
<tr>
<td>LCCSCT</td>
<td>large-cell calcifying Sertoli cell tumor</td>
</tr>
<tr>
<td>NMD</td>
<td>nonsense mediated mRNA decay</td>
</tr>
<tr>
<td>PPNAD</td>
<td>Primary-pigmented nodular adrenocortical disease</td>
</tr>
<tr>
<td>PKA</td>
<td>protein kinase A</td>
</tr>
<tr>
<td>cAMP</td>
<td>cyclic adenosine monophosphate</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>GH</td>
<td>growth hormone</td>
</tr>
<tr>
<td>oGTT</td>
<td>oral glucose tolerance test</td>
</tr>
<tr>
<td>TRH</td>
<td>thyrotropin-releasing hormone</td>
</tr>
<tr>
<td>\textit{PRKAR1A}</td>
<td>type 1A of protein kinase A</td>
</tr>
<tr>
<td>IgF-1</td>
<td>Insulin-like growth factor 1</td>
</tr>
</tbody>
</table>

* Corresponding author.

E-mail address: jerome.bertherat@cch.aphp.fr (J. Bertherat).

\textsuperscript{1} Delphine Vezzosi has a fellowship from Institut National du Cancer.
by Carney et al. [1]. It is an autosomal dominant multiple endocrine neoplasia although sporadic cases may account for up to one-third of affected individuals. The exact prevalence of CNC is difficult to establish but this is clearly a rare disease with no more than 750 cases from many ethnicities reported worldwide since 1985, when the disease was first described. However, this prevalence can be underestimated because the diagnosis can be challenging and the awareness of this rare and complex disorder is limited among the medical community.

The endocrine and nonendocrine manifestations of CNC can be numerous and vary between patients. These include myxomas of the heart, skin and breast, testicular, adrenocortical and GH secreting pituitary tumors, schwannomas. In general, families with CNC tend to have similar groupings of manifestations, although some families exhibit variability. Also, CNC families can exhibit only one tumor type, as isolated PPNAD or isolated cardiac myxomas [2]. The estimated frequency of these manifestations is listed in Table 1.

The diagnosis criteria for CNC were reviewed in 2001 and are provided in Table 2 [3]. Diagnosis is based on the presence of two or more cardinal manifestations confirmed by histology,

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Finding</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Lentiginosis</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Other nevi or skin lesions</td>
<td>50</td>
</tr>
<tr>
<td>Myxoma</td>
<td>Cardiac</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>Extracardiac</td>
<td>20</td>
</tr>
<tr>
<td>Endocrine tumor</td>
<td>PPNAD</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Acromegaly</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Thyroid nodules</td>
<td>25</td>
</tr>
<tr>
<td>Gonadal tumors</td>
<td>Testicular tumor</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>Ovarian cysts</td>
<td>14</td>
</tr>
<tr>
<td>Neural crest</td>
<td>Schwannoma</td>
<td>5</td>
</tr>
<tr>
<td>Breast</td>
<td>Breast ductal adenoma</td>
<td>20</td>
</tr>
<tr>
<td>Bone</td>
<td>Osteochondromyxoma</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

Table 2
Diagnostic criteria for Carney complex and findings suggestive of a possible association with Carney complex but not diagnostic for the disease.

Major diagnostic criteria for CNC
- Spotty skin pigmentation with typical distribution (lips, conjunctiva and inner or outer canthi, vaginal and penile mucosa)
- Myxoma (cutaneous and mucosa)\(^a\)
- Cardiac myxoma\(^a\)
- Breast myxomatosis\(^a\) or fat-suppressed magnetic resonance imaging findings suggestive of this diagnosis
- Primary-pigmented adrenocortical disease\(^a\) or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddle’s test
- Acromegaly due to GH-producing adenoma\(^a\)
- Large-cell calcifying Sertoli cell tumor\(^a\) or characteristic calcification on testicular ultrasound
- Thyroid carcinoma\(^a\) or multiple, hypoechogenic nodules on thyroid ultrasound in a young patient
- Psammomatous melanotic schwannomas\(^a\)
- Blue nevus, epithelioid blue nevus\(^a\)
- Breast ductal adenoma\(^a\)
- Osteochondromyxoma\(^a\)

Supplementary criteria
- Affected first-degree relative
- Inactivating mutation of the PRKARIA gene

Findings suggestive of or possibly associated with CNC but not diagnosis for the disease
- Intense freckling (without darkly pigmented spots or typical distribution)
- Blue nevus, common type (if multiple)
- Café au lait spots or other birthmarks
- Elevated IGF1 levels, abnormal oGTT or paradoxical GH response to TRH testing in the absence of clinical acromegaly
- Cardiomyopathy
- Pilonidal sinus
- History of Cushing syndrome, acromegaly or sudden death in extended family
- Multiple skin tags or other skin lesions; lipomas
- Colonic polyps (usually mild and almost always combined with clinical or subclinical acromegaly)
- Hyperprolactinemia (usually mild and almost always combined with clinical or subclinical acromegaly)
- Single, benign thyroid nodule in a young patient; multiple thyroid nodules in an older patient (detected on ultrasound)
- Family history of carcinoma, in particular of the thyroid, colon, pancreas and ovary; other multiple benign or malignant tumors

Adapted from [3] (adapté de [3]).

CNC: Carney complex; GH: growth hormone.
\(^a\) After histological confirmation.
biochemical testing or imaging. If the patient has a demonstrated germ line PRKAR1A mutation and/or a first-degree relative affected by CNC, a single manifestation is sufficient for the diagnosis.

Once the diagnosis is demonstrated, the patient will require life-long surveillance. Clinical work-up for all the manifestations of CNC should be performed at least once a year in all patients and should start in infancy for some manifestations. This review intends to present the current knowledge about the clinical and genetic aspects of the disease and to discuss its management.

3. Molecular genetics of Carney complex

The first report of Carney complex in 1985 [1] suggested already its autosomal dominant inheritance. Then, the genes responsible have been mapped to 17q22-24. In tumors from CNC patients of families mapping to 17q, loss of heterozygosity was helpful to precise the location of the CNC1 gene [4].

3.1. PRKAR1A and the 17q22-24 locus

The CNC1 gene located at 17q22-24 has been reported 10 years ago as encoding the regulatory subunit PRKAR1A [4,5].

PKA is a 3′,5′ cAMP-dependant protein kinase and a main mediator of cAMP signalling. It is therefore a key and ubiquitous enzyme controlling various cellular functions. For instance, it plays a major role in peptide hormone signalling and endocrine tissue activity. PKA is an heterotetrameric enzyme, composed of two regulatory and two catalytic subunits [6]. Elevation in the intracellular cAMP levels and, consequently, binding of cAMP to PKA lead to dissociation of the free catalytic subunits from the regulatory subunits. This leads to stimulation of PKA activity. Indeed, in its free active form, the catalytic subunits can phosphorylate a series of target that regulate downstream effectors enzymes, ion channels, and activate the transcription of specific genes mediating the cell growth and differentiation [7]. PRKAR1A, one of the regulatory subunit, is the most widely and highly expressed of the four subunits and it has been shown that it may be able to compensate for the loss of other subunits [8].

Heterozygous inactivating mutations of PRKAR1A were reported in 45 to 73% of CNC families [2,3,9,10]. Thus, genetic analysis should be proposed to all CNC index cases. Moreover, when a PRKAR1A gene mutation is identified, a genetic analysis should be proposed to all first-degree relatives.

PRKAR1A mutations could be located in all the coding exons and adjacent introns of the gene (Fig. 1). Most of the known PRKAR1A mutations are point or small mutations involving up to 15 bp affecting the coding region of the gene, including nonsense, frameshift and splice site mutations [9]. However, larger gene deletions have been described in small number of cases [11].

Mutations that lead to the expression of an abnormal, defective PRKAR1A protein are much less frequent [10–14] and tend to be associated with an aggressive phenotype 2, [11,12]. NMD PRKAR1A mutations are more frequent (80%) [2,3]. They result from the occurrence of a premature stop codon that lead to degrada-

![Fig. 1. PRKAR1A mutations. Schematic presentation of the location of the 113 known germ line reported PRKAR1A mutations. The two hot-spots are indicated.](image)

Adapted from [56] (Adapté de [56]).
hypercortisolism [18,19]. Recently, mice lacking R1A specifically in the adrenal cortex have been generated. These mice develop autonomous adrenal hyperactivity and bilateral adrenal hyperplasia [20].

Initial data supported the role of PRKAR1A as a tumor suppressor gene with tumors from CNC patients exhibiting germ line mutations and subsequent loss of heterozygosity at the PRKAR1A locus 12. However, the precise mechanism of tumorigenesis remains controversial as it now appears that haploinsufficiency of PRKAR1A may be sufficient for phenotypic expression of increased PKA activity [21] and the development of certain tumors such as eyelids myxomas [8].

3.2. 2p16 locus

Somatic alterations of a second putative CNC locus at 2p16 have been reported in CNC tumors, even in patients with PRKAR1A gene mutations [22]. These alterations are usually loss of heterozygosity and copy number gains, suggesting that this gene can be a potential oncogene. However, sequencing of candidate genes of the 2p16 region in the linked families did not reveal yet alterations [9,23].

3.3. Phosphodiesterases genes

PDE8B and PDE11A belong to the huge family of phosphodiesterases comprised by 21 so far identified genes that are classified in 11 different families. They are expressed in several endocrine tissues including adrenal cortex. Recently, inactivating mutations of PDE11A and more rarely PDE8B have been observed in patients with isolated micronodular pigmented (PPNAD) or nonpigmented hyperplasia [24–27]. These mutations resulted in premature stop codon generation or in single-base substitutions in the catalytic domain of the protein [28].

4. Carney complex manifestations

4.1. Endocrine glands and gonads

4.1.1. Cushing syndrome and primary pigmented nodular adrenocortical disease

From an endocrine point of view, the most common manifestation of CNC is PPNAD, a cause of ACTH-independent Cushing syndrome. Although autopsies summaries report constant histological evidences for PPNAD, only 60 to 70% of CNC patients exhibit Cushing syndrome. The disease was named after the macroscopic appearance of the adrenal cortex that is characterized by the small-pigmented nodules less than 10 mm in their greatest diameter most often surrounded by atrophic cortex [29]. The disease is bilateral with primary involvement of both adrenals. Cushing syndrome due to PPNAD is more frequent in females and mostly observed in young adults, with a peak during the second and third decade of life. Clinical signs are similar to those observed in patients presenting with other causes of hypercortisolism. However, it needs to be kept under constant vigilance as clinical manifestation can sometimes be subtle and can nonetheless lead to significant metabolic effects over time. In contrast, cyclic forms of hypercortisolism can be observed with large and rapid burst of cortisol excess, which might spontaneously regress [30–32]. Urinary cortisol is increased in most patients but its levels can be variable. The circadian rhythm of cortisol secretion is usually completely abolished. Dexamethasone fails to suppress cortisol secretion even after high dose administration. In addition, most of the patients respond to dexamethasone with a paradoxical rise of cortisol production [31]. This test may be used diagnostically for the identification of PPNAD, even in patients that have normal baseline cortisol levels and do not have clinical stigmata of Cushing syndrome. Plasma ACTH levels are low.

Adrenals appear normal on CT-scan in one out of three of the patients whereas the other patients present with micronodules (usually less than 6 mm) or more rarely macronodules larger than 10 mm [33]. Pathological investigation demonstrates that adrenal glands are usually normal in size and weight and are peppered with black or brown nodules set in a cortex that is often atrophic.

Cushing syndrome due to PPNAD requires treatment to control the consequences of cortisol oversecretion. Bilateral adrenalectomy is the most common treatment although under certain circumstances, ketoconazole or mitotane has been used as anticoletic treatment.

4.1.2. Pituitary

Pituitary tumors typically involve the GH-producing cells and cause acromegaly. Acromegaly in CNC has usually a slow, progressive course. It does not appear until the third decade of life [34,35]. Clinical acromegaly is uncommon, being seen in approximately 10 to 15% of patients. However, prevalence of biochemical abnormalities of the GH axis as alterations in the rhythm of GH secretion may be higher if carefully screened, up to 80% of the patients [34]. These biochemical abnormalities develop before radiological evidence of a frank pituitary tumor and might be secondary to hyperplasia of GH cells, characterized at pathological examination by poorly delineated regions with increased cellularity [36].

Few Carney patients with acromegaly have an aggressively growing tumor that will require surgery followed or not with irradiation treatment [34]. Treatment of acromegaly with somatostatin analogs may also be used either as a primary treatment or as an adjuvant to surgery. Most of the remaining patients have abnormal responses to oGTT but normal IGF-1 (Insulin-like growth factor 1) and normal pituitary imaging. These latter patients can be followed by magnetic resonance imaging and oGTT. If a tumor develops, it is treated surgically, whereas if IGF-1 levels increase without a visible tumor, somatostatin analogs or GH receptor antagonist treatment can be discussed.

Prolactinomas have also been reported in a small number of patients but they are most often not isolated but associated with GH adenomas [36]. Moreover, pathologic findings reveal that it is the same cellular population that demonstrated immunoreactivity for both GH and prolactin. Staining for α-subunit was also present in most tumors in the same pattern as that of prolactin. TSH, LH, ACTH and FSH staining when obtained, is usually
been seen only in foci of normal pituitary cells entrapped within the tumors or the hyperplasia.

4.1.3. Thyroid tumors
Thyroid nodules are fairly common in CNC patients. By sonographic examination, up to 75% of patients are found to have cystic or multinodular disease [37]. Thyroid nodules are most often benign, nontoxic adenomas, mostly of follicular type. Thyroid cancer is observed in about 3% of the patients. It is most often papillary carcinoma that can be multiple and sometimes quite aggressive indicating the need for chronic surveillance of the thyroid. Thus, for post-pubertal pediatric and adult patients, an annual clinical examination associated when required with a thyroid ultrasound is recommended. Fine needle investigation of the thyroid nodule can also be helpful.

4.1.4. Gonadal tumors
Patients may exhibit ovarian tumor or testicular tumors [38]. They are rarely malignant but a small number of cancers have been reported. For post-pubertal pediatric and adult patients, an annual clinical examination associated with a gonad ultrasound is recommended.

4.1.5. Testicular lesions
The testicular tumors can be of three types: Large-cell calcifying Sertoli cell tumor (LCCST), nodular adrenocortical rests and Leydig cell tumors [3,1]. Up to 20 to 50% of Carney patients have one or more of these masses.

As a sporadic neoplasm, LCCST, a stromal benign tumor, is among the rarest of lesion tumor whereas it occurs frequently in male patients with CNC [39]. LCCST may be bilateral and multifocal in about 50% of the patients [40]. They are easily detected by ultrasound investigation as bilateral microlcifications. They progress gradually with age to replace the normal testicular tissue. As they can cause replacement and obstruction of seminiferous tubules, they can be the cause of reduced fertility observed in men with CNC. Malignant changes have been rarely described particularly when the primary tumor is large, above 6-cm diameter [41].

Nodular adrenocortical rests and Leydig cell tumors are less observed.

These three types of tumor are frequently asymptomatic. However, precocious puberty or male feminization have been rarely reported [39,41,42].

As these masses are often asymptomatic and not palpable, testicular ultrasound is routinely recommended in a patient diagnosed with CNC.

Apart from the tumoral aspects, recent data suggest that sperm abnormalities are present in CNC. Knockout male mice heterozygous for PRKARIA have severely reduced fertility, and these mice as well as CNC patients have morphologically abnormal sperm and reduced spermatozoïd number [43,44].

4.1.5.1. Ovarian tumors. Women with CNC commonly develop ovarian cysts and tumors of the ovarian surface epithelium including serous cystadenomas and cystic teratomas. These lesions are easily found by sonographic examination as multiple hypoechoic lesions [38]. They can grow and require in that case surgery. Ovarian lesions were described at autopsy in about 60% of the patients. Ultimately, they may progress occasionally to ovarian carcinoma (mucinous adenocarcinoma or endometrioid carcinoma) usually during their fifth decade of life.

Thus, although ovarian tumors do not seem to be a major manifestation of CNC, sonography of the ovaries may be part of the initial evaluation in women with CNC. Follow-up of any identified lesion is recommended because of the possible risk for malignancy.

4.2. Cardiac myxomas
Cardiac myxomas are benign neoplasms almost equally distributed among the ages and the sexes. They are found in about 20 to 40% of Carney patients. Unlike sporadic tumor, CNC-associated myxomas can be located within any chamber of the heart and can be multiple. They can be the cause of stroke due to embolism and cardiac deficiency. They require surgical removal. However, they can recur despite seemingly adequate excision, thus rendering surgical cure problematic.

These tumors are the most frequent cause of death in CNC patients, either related to the tumors themselves or to surgical complications that occur during or after their removal. It may be the cause of the high rate of sudden death historically reported in CNC patients. As a consequence, early diagnosis of these tumors is important and should start in the first 6-months of life with annual screening by cardiac ultrasound. In patients with a history of cardiac myxomas, screening should be performed every 6 months. In difficult cases, transesophageal ultrasound and cardiac magnetic resonance imaging can be helpful (Fig. 4).

4.3. Skin lesions
Skin manifestations are heterogeneous but are very frequent and their onset is early in patients with CNC facilitating the identification of the disease by the dermatologist. Patients with CNC do not appear to have a clear predisposition for skin cancers.

From a clinical point of view, the most commonly manifestation of CNC is lentiginosis as they are reported in about 50 to 80% of patients with CNC. Other skin lesions such as multiple blue nevi, café au lait spots and cutaneous tumors (myxomas or fibromas) are reported in about 50% of the CNC patients.

Lentiginosis are typically flat, poorly circumscribed, brownish to black macules located around the lips, on the eyelids, ears and the genital area (Fig. 2). They usually are small (<5 mm) and do not change with sun exposure. The density of pigmented spots can vary from a few lesions to diffuse pigmentation. Lentiginosis is one of the manifestations of CNC that occur earlier. It may be observed at birth in some cases and often appears during childhood and the prepubertal period. Lentigines usually do not acquire their typical intensity and distribution until the peripubertal period [2,45,46]. CNC-lentigines were difficult to distinguish from solar lentigines in many cases. However, in contrast to the age-related skin lesions, CNC associated lentigines tend to fade after the fourth decade of life although they may
be appreciable as late as the eighth decade [45,46]. Moreover, they are not found exclusively on sun exposed areas.

Blue nevi are, after lentigines, the second most frequent skin lesions in patients with CNC as they are observed in about 40% of patients [46]. They are small, blue to black-colored marks with circular or star-shaped appearance and their distribution are variable.

The third most common skin manifestation of CNC is cutaneous myxoma as they are reported in 20 to 55% of patients [2,46]. However, this percentage is likely to underestimate the true incidence of these lesions because not every skin lesions in every patient was biopsied. They typically appear before the age of 18 years and have a tendency to recur. The lesions vary between asymptomatic, sessile, small (rarely exceeding 1 cm in diameter), opalescent or dark pink papules and large, finger-like, pedunculated lesions (Fig. 3). They can occur anywhere but usually affect the eyelids, ears, nipples, external ear canal, trunk and perineum. Myxoma is the most specific dermatological criterion for CNC diagnosis. They can be used for the early detection of the disease and, thus, the prevention of life-threatening complications of CNC related to heart myxomas and endocrine abnormalities. For instance, it is estimated that approximately 80% of the CNC patients with cardiac myxomas presents with cutaneous myxomas earlier in life [2,46].

Finally, café au lait spots or other birthmarks (depigmented lesions) can also be observed. They are rarely present as an isolated skin manifestation of CNC and can be present at birth.

To date, the molecular causes underlying the formation of pigmented skin lesions in CNC are not fully understood. A possible mechanism involves the PKA-mediated activation of pathways downstream of the melanocortin receptors that form a subfamily of the G-protein-coupled receptors and regulate a wide variety of processes, including skin pigmentation [47–49].

4.4. Breast lesions

Breast tissue characteristic lesions in CNC include lobular or nodular myxomatosis, myxoid fibroadenomas or ductal adenomas [50,51]. They are often bilateral and occur in 20% of the female patients [2]. However, this percentage is likely to underestimate the true incidence of these lesions because breast magnetic resonance imaging was performed in only a small number of the patients. Treatment and follow-up of these lesions are not well standardized.

4.5. Psammomatous melanotic schwannoma

Pigmented melanotic schwannoma, derived from the schwann cells of the nervous system can be observed in about 5 to 10% of patients with CNC. These pigmented tumors which can be mistaken for malignant melanomas demonstrate spindle cell morphology but exhibit clinical characteristics of schwannomas. They presented with frequent calcifications and multicentricity. They can be observed anywhere in the central or peripheral system but their most frequent site are the gastrointestinal tract.
4.6. Bone lesions: osteochondromyxoma

Osteochondromyxoma is a rare component of Carney complex that have been diagnosed in no more than 10% of the patients [52]. They occur early in life, usually before the age of 2, when sporadic bone tumors are rare. Clinically, the tumors are painless masses that occurred in distal long bones (diaphyseal) and small flat bones (nasal). Osteochondromyxoma are usually benign but local invasiveness has often been observed.

Complete excision of the lesion, when possible, should be curative. Incomplete removal is likely to be followed by local recurrence.

4.7. Other lesions

Other lesions can be associated with Carney complex but are less frequent as hepatocellular carcinoma [53], intraductal papillary mucinous tumor of the pancreas [54] or multiple fusiform myxomatous cerebral aneurysms [55].

5. Conclusion

Carney complex is a rare disease leading to numerous endocrine and nonendocrine lesions. During the last decade, numerous progresses have been done to improve diagnosis, treatment and follow up of Carney patients. However, because of the rarity and the various manifestation of CNC, Carney patients need to be followed in reference centers with a multidisciplinary approach. Moreover, prospective studies will be important to develop evidenced-based recommendations for the screening schedule and therapeutic guidelines for better disease management.

Conflicts of interest statement

The authors have not declared any conflicts of interest.

References


