European Journal of Medical Genetics 63 (2020) 103873

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: www.elsevier.com/locate/ejmg

Revised Danish guidelines for the cancer surveillance of patients with Cowden Syndrome

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ARTICLE INFO

Keywords:
Cowden syndrome
PTEN
Management guidelines
Cancer

ABSTRACT

Introduction: Cowden syndrome is a cancer predisposition syndrome caused by pathogenic variants in *PTEN*. The affected patients possess an increased risk of breast, thyroid, renal, colorectal, endometrial cancers as well as malignant melanoma. Thus prophylactic surveillance and follow up is crucial for these patients.
Methods: A review of the literature including existing guidelines from the years 1996 until 2017 was carried out. In total, 2078 scientific papers were identified through database searches on Cowden syndrome. Among these, 11 manuscripts were included based on scientific relevance and quality.
Expert consensus was reached to define management guidelines.
Results: The literature revealed a high risk of cancer in specific organs for patients diagnosed with Cowden Syndrome. Alternative management guidelines were proposed and discussed.
Conclusions: Here we propose a revised set of management guidelines for patients with Cowden syndrome in Denmark to address the increased risk of various cancer types.

1. Background

Cowden Syndrome is a hereditary multi-system disorder encompassed by the term PHTS (*PTEN* Hamartoma Tumor Syndrome). The syndrome is characterized by multiple hamartomas as well as an increased risk of both malignant and benign manifestations compared to non-affected persons. The increased risk of malignancy includes breast, thyroid, endometrial, colorectal and renal cancers as well as malignant melanoma (Tan et al., 2012). The risk of benign manifestations includes macrocephaly and mucocutaneous lesions. Furthermore, an association with autism and seizures has also been suggested, albeit the mechanism is not yet fully elucidated (Tilot et al., 2015) (Conti et al., 2012).

Previous reports approximate that Cowden Syndrome affects 1 in 200,000 individuals. This number is probably underestimated due to the diverse presentation of the syndrome, delayed diagnosis and limited awareness of the condition (Nelen et al., 1999). In 1963, the first case of Cowden Syndrome was described. A 20 year old woman presented with breast ulcerations, multinodular goiter, papillomatosis of the tongue and oral mucosa. She died in her 30ties of metastatic breast cancer (LLOYD and DENNIS, 1963). In 1996 the International Cowden Consortium published criteria to aid diagnosis (Nelen et al., 1996) (Eng, 1997). Today, NCCN (National Cancer Comprehensive Network) has published evidence based diagnostic guidelines which have been updated during the years and are now used worldwide (Pilarski et al., 2013) (NCCN, 2019).

Cowden Syndrome is caused by pathogenic variants in *PTEN*, a gene mapped to chromosome 10q23.3. (Nelen et al., 1996). The *PTEN* gene encodes a 403 amino acid dual-specificity phosphatase which acts as a tumor suppressor in the PI3K/AKT/mTOR pathway. Pathogenic variants promote an upregulation of the AKT pathway leading to decreased apoptosis and increased cell growth (Mester and Eng, 2013).

The *PTEN* disorders are autosomal dominantly inherited. Previous studies have reported pathogenic germline *PTEN* variants in 80% of

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https://doi.org/10.1016/j.ejmg.2020.103873
Received 20 February 2019; Received in revised form 5 November 2019; Accepted 1 February 2020
Available online 10 February 2020
1769-7212/

Table 1
NCCN (version 2.2017) diagnostic criteria for Cowden Syndrome: Three or more major criteria, including macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or two major and three or more minor criteria as proposed by Pilarski et al. (2013)

Major criteria	Minor criteria
• Breast cancer • Endometrial cancer epithelial • Thyroid cancer follicular • GI hamartomas (including ganglioneuromas but excluding hyperplastic polyps; ≥3) • Lhermitte-Duclos disease (adult) • Macrocephaly (megalocephaly) (ie, ≥97%, 58 cm in adult woman, 60 cm in adult men • Macular pigmentation of glans penis • Multiple mucocutaneous lesions • Multiple trichilemmomas (≥3, at least one biopsy-proven) • Akral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules) • Mucocutaneous neuromas (≥3) • Oral papillomas (particularly on tongue and gingiva), multiple (≥3) OR biopsy proven OR dermatologist diagnosed	• Autism spectrum disorder • Colon cancer • ≥3 Esophageal glycogenic acanthoses • ≥3 Lipomas • Intellectual disability (ie, IQ ≤ 75) • Papillary or follicular variant of papillary thyroid cancer • Thyroid structural lesions (Eg, adenoma, multinodular goiter) • Renal cell carcinoma • Testicular lipomatosis • Vascular anomalies (including intracranial developmental venous anomalies)

Cowden patients whereas newer literature report pathogenic variants in *PTEN* in 25% of affected individuals (Marsh et al., 1998) (Tan et al., 2011). Whether this is due to diagnosing without a genetic verification, or vague diagnostic criteria, remains to be elucidated.

Up to 47% of Cowden Syndrome cases are suggested to be caused by *de novo* variants in *PTEN* (Mester and Eng, 2012).

Due to the increased risk of malignancy, it is crucial that patients diagnosed with Cowden Syndrome enter and follow a surveillance program tailored to the characteristics of the disease. We emphasize, that this guideline only comprises Cowden Syndrome patients with an identified pathogenic variant in *PTEN* or who comply with the diagnostic criteria given by the NCCN.

Patients who harbor a pathogenic variant in *PTEN*, but do not have any symptoms or signs of Cowden syndrome should still be offered surveillance, without receiving the clinical diagnosis. Patients only fulfilling some of the diagnostic criteria for Cowden Syndrome should be offered screening of a relevant genetic panel, including *PTEN*. If no pathogenic variant is detected, another diagnosis should be considered based on the specific symptoms of the patient. It is important to notice that the patient might not present with all the clinical manifestations yet, but Cowden syndrome can develop with age. Thus, the age of the patient at the time of the investigation should also be taken into consideration.

Similarly, diagnosing children with Cowden syndrome according to the NCCN diagnostic criteria is complicated by the age related penetrance of most of the clinical findings.

Cowden Syndrome has a clinical overlap with several other cancer predisposition syndromes, the exact phenotype and risk estimates of those are beyond the scope of the current paper.

Proposing management guidelines is always a challenge, and many questions need to be addressed; is the existing literature at a satisfying scientific level? What is the risk threshold for recommending surveillance, considering the drawbacks of secondary sequelae to the examination, radiation doses, false positive findings and subsequently psychological harm etc.? Socioeconomic issues and the inconvenience for the patients need consideration as well. Especially, with regards to surveillance of children, screening programs often offer a trade-off between the benefits of protection, against a risk of stigmatization. These considerations are incorporated in our proposals.

Due to the rarity of Cowden Syndrome, all management guidelines so far, are based on observational studies rather than randomized clinical studies. One ought to bear this in mind when introducing the surveillance program to the patients. These guidelines introduce improvements compared to previous surveillance guidelines, especially with regards to young patients and the attempt to identify potential neoplasms as early as possible.

The focus of this work is mainly on cancer surveillance and only to a smaller extent, on other manifestations of Cowden Syndrome. In 2012, Skytte AB et al. proposed the existing Danish guidelines for the management of Cowden Syndrome (Skytte et al., 2014). However, as our understanding of *PTEN*-related disease and the management hereof is still evolving, we find it necessary to update the current guidelines. Thus, the aim of this paper is to revise and improve the management of Cowden Syndrome patients according to the latest literature.

2. Methods

This work is based on a systematic search at PubMed using the search terms “Cowden Syndrome AND cancer” and “PTEN hamartoma tumor syndrome AND cancer”. Search filters included “case reports”, “clinical trials”, “letters”, “reviews” and “journal articles”. Publication date filter was January 1st, 1996 until July 1st, 2017. Text availability was limited as “full text” and species were identified as “humans”. Only literature in English was assessed. The number of hits for each search criteria was 1082 and 984, respectively, and additional 12 records were identified through other sources, mainly reviews. Based on the titles, scientific papers concerning cancer in patients with Cowden syndrome were selected for review. Papers of poor scientific quality were excluded from the analysis. In addition, a single paper from 1986 was included as well, based on its high relevance for this review. In total 11 studies were included.

3. Cancer risk

A number of studies have demonstrated a significantly increased risk of several types of cancer for patients harboring a pathogenic *PTEN* variant or fulfilling the diagnostic criteria of Cowden Syndrome (Tan et al., 2012) (Bubien et al., 2013) (Nieuwenhuis et al., 2014) (Heald et al., 2010). Characteristics and specifications for the three main references cited in these guidelines are listed in Table 2.

4. Breast cancer

In 1986 Starink et al. published a prevalence of breast cancer of 25–50% in a relatively young (half of them were below 50 years of age at the time of the investigation) cohort of women with Cowden Syndrome. Today this is well established and one of the most characteristic features of Cowden Syndrome (Starink’ et al., 1986). Interestingly, a few cases of male breast cancer have been observed as well, but an elevated risk has not been established (Fackenthal et al., 2001).

The elevated risk of breast cancer in women has been verified by three recently published papers. Tan et al. investigated a cohort of more than 3000 patients of whom 295 were identified with a germline deleterious variant in *PTEN* and additional 73 patients were identified with pathogenic *PTEN* variants following screening of the relatives. They demonstrated a breast cancer life time risk for women of 85% and

Table 2
The three main references and their characteristics. Table with inspiration from Mester and Eng, 2015 J. Surgical Oncology.

	Tan et al., (2012)	Bubien et al., (2013)	Nieuwenhuis et al., (2014)	
Method	3399 participants meeting ICC [a] criteria had *PTEN* mutation search. 368 patients had a pathogenic variant in *PTEN*	Between 1997 and 2008, 546 patients were referred for *PTEN* mutation search. 146 patients had a pathogenic variant in *PTEN*	Clinical genetic centres contributed with data on patients proven with a pathogenic variant in *PTEN*. 180 patients had a pathogenic variant in *PTEN*	
Number of patients	*368*	146	180	
Male	*163*	76	81	
Female	*205*	70	99	
Median age (years)	39	36	32	
Lifetime cancer risks				
Any cancer	N/A	85%	Male: 56%	Female: 87%
Breast cancer	85%	77%		67%
Thyroid cancer	35%	38%	Male: 6%	Female: 25%
Renal cancer	34%	48.9 (5.5–176.6) [b]	Male: 2%	Female: 9%
Endometrial cancer	28%	48.7 (9.8–142.3) [b]		21%
Colorectal cancer	9%	6.7 (0.09–37.1) [b]	Male: 20%	Female: 17%
Melanoma	6%	28.3 (7.6–35.4) [b]	Male: 2%	

[a] ICC-International Cowden Consortium Criteria.
[b] SIR (95%CI): No. of cases too small for further statistical analysis, female cohort figures.

their age related penetrance curve showed that the risk started to elevate at the age of 30 (Tan et al., 2012). In comparison, the life time risk of sporadic breast cancer in the northern countries is 10% (Danckert et al., 2019a).

Bubien et al. also evaluated the risk of breast cancer in a cohort with deleterious *PTEN* variants and the results were in line with those from Tan et al. with a lifetime risk estimate of breast cancer of 77% by the age of 70 years (Bubien et al., 2013).

Similar results emerged in the published data from Nieuwenhuis et al., who estimated a life time risk at 60 years of 67% based on a cohort with germline *PTEN* variants (Nieuwenhuis et al., 2014). Banneau et al. showed a mean age of 42 years (27–59) of the first diagnosis of breast cancer (Banneau et al., 2010).

Bubien et al. suggested that contralateral breast cancer is seen in 50% of women with Cowden Syndrome; furthermore, Ngeow et al. showed that within 10 years from the first breast cancer, 28% of women with Cowden Syndrome developed a secondary breast cancer (Bubien et al., 2013) (Ngeow et al., 2014). In comparison, the annual risk of contralateral breast cancer for the general population receiving standardized adjuvant therapy is 0.2–0.5%, confirming, that factors contributing to the risk of contralateral breast cancer comprises gene mutation status (Boughey et al., 2016).

As noted by Tan et al., these data clearly indicate a significant increased life time risk of breast cancer similar to the risk seen in pathogenic *BRCA* variant carriers. Therefore, surveillance should resemble the program recommended for patients with a high risk of breast cancer, as also suggested by Mester et al. (Tan et al., 2012) (Mester and Eng, 2015). Thus, we recommend annual clinical mammography (clinical examination, ultrasound and mammography) being initiated at 30 years and with the possibility of accompanying MR scans. Based on the high risk of breast cancer, prophylactic bilateral mastectomy can be an option after thorough information from surgeons and geneticists.

5. Thyroid cancer

Thyroid cancer is another malignancy associated with pathogenic *PTEN* variants and Cowden Syndrome. Epithelial thyroid cancer is seen in 1/3 of patients with pathogenic *PTEN* variants or a clinical Cowden Syndrome diagnosis (Tan et al., 2012). Papillary thyroid cancer as well as follicular variant of papillary cancer is the most frequent pathology. However, follicular thyroid cancer is overrepresented in patients with *PTEN* mutations compared to the general population and is therefore one of the major diagnostic criteria (see Table 1) (Pilarski et al., 2013).

Thyroid cancer may arise in an otherwise normal thyroid gland and may be preceded by multinodular goiter. Other benign thyroid manifestations such as solitary nodules or Hashimotos thyroiditis are seen in 50–70% of patients with Cowden Syndrome (Milas et al., 2012) (Pilarski, 2009).

Tan et al. demonstrated a life time risk estimate of 35% and Bubien et al. a life time risk estimate of 38% (Tan et al., 2012) (Bubien et al., 2013). Milas et al. showed that 32 out of 225 patients harboring pathogenic *PTEN* variants with a mean age of 32 years at the time of consent for the study had thyroid cancer (Milas et al., 2012).

The current literature demonstrates an elevated risk of thyroid cancer compared to the background population. Thus, although there is no evidence of a beneficial effect, we suggest annual surveillance preferably with physical examination and ultrasound of the thyroid. In case of total thyroidectomy, the surveillance should be discontinued.

One of the clinical challenges is how to examine and follow the patients with one or more nodules, which is a common finding in the background population after the age of 18 (Knudsen et al., 2000). Even with ultrasound and clinical examination of the thyroid, benign and malignant nodules can be difficult to distinguish. Consequently, several biopsies might be needed with a high possibility of false positive, false negative or inconclusive findings (Gharib et al., 2010).

The youngest patient reported to date suffering from thyroid cancer was 7 years old (Smith et al., 2011), and additional cases of thyroid cancer in children have been described (Ngeow et al., 2011). However, the initiation of surveillance is controversial. The NCCN guidelines recommend thyroid ultrasound from the time of discovery of a pathogenic *PTEN* variant while others advocate for ultrasound starting in adulthood (Schreibman et al., 2005) (Milas et al., 2012) (Mester et al., 2012).

Based on the literature, the risk of false positive findings as well as the relatively low risk of thyroid cancer in childhood, we recommend that pathogenic *PTEN* variant detection entails annual surveillance from the age of 15, including both physical and ultrasound examination of the thyroid. Furthermore, a multidisciplinary team consisting of an endocrinologist, an ENT-surgeon and a clinical geneticist should discuss the advantages and disadvantages of early thyroidectomy. Details of comorbidity, family history, and the *PTEN* analysis results should be taken into consideration. The conclusions should be shared with the patient by the relevant clinician.

6. Renal cell carcinoma

Renal cell carcinoma (RCC) is one of the minor criteria in NCCNs diagnostic criteria for Cowden Syndrome. However, literature on this

specific topic is sparse. Tan et al. reported a life time risk estimate for RCC of 34% and suggested a surveillance program with ultrasound or MRI biannually from the age of 40 (Tan et al., 2012). Men and women had a median age of 39 years, however, information about the age of the affected patients is limited and hence, this risk should be interpreted with caution. Shuch et al. showed that only 4 out of 24 patients with Cowden syndrome (confirmed by the clinical diagnostic criteria and mutational screening) had a personal history of RCC. However, the age of the patients at follow-up was unknown (Shuch et al., 2013). The patients with RCC were 32, 53, 56 and 57 years at the time of diagnosis (Shuch et al., 2013). The two studies are not comparable, since their methodology differs significantly.

Both papillary and chromophobe RCC is seen in patients with Cowden Syndrome (Mester et al., 2012).

Further investigations are certainly needed regarding the association between Cowden Syndrome and RCC, but meanwhile, we recommend ultrasound or MRI of the kidneys every second year from the age of 40. If renal cell carcinoma is diagnosed in the family surveillance should be initiated 10 years before the age of the youngest affected family member.

7. Endometrial cancer

The life time risk of endometrial cancer in the general female population is 2% (Danckert et al., 2019b). The current risk estimates for Cowden Syndrome are inconsistent. However, the life time risk is considered increased. Published data reveal life time risk estimates of 19–28% indicating that further validation is needed (Riegert-Johnson et al., 2010) (Tan et al., 2012). Riegert-Johnson et al. estimated a life time endometrial cancer risk of 19% at 70 years. While Bubien et al. reported that endometrial cancer was overrepresented (Bubien et al., 2013). It is worth mentioning that these patient cohorts were collected from the literature, introducing selection bias. Furthermore, the cohort size differs, since 368 were included in the study by Tan et al., which is more than twice the patients included in the two other studies by Riegert-Johnson et al. and Bubien et al.

The risk of endometrial cancer is reported to increase from the age of 25 (Tan et al., 2012). However, at least two case reports of endometrial cancer in adolescence have been published (Schmeler et al., 2009) (Baker et al., 2013).

Currently, NCCN recommends consideration of annual endometrial biopsies and/or ultrasound from the age of 30–35. In addition, they encourage education of the patients and a prompt response to symptoms (NCCN, 2019), such as bleeding but also weight loss, pain, dyspnea and ascites. Furthermore, a discussion to opt for hysterectomy is advised.

Our proposed surveillance recommendations include annual transvaginal ultrasound possibly supplemented with endometrial biopsy from the age of 30–35 or 5–10 years prior to the age at the time of diagnosis of affected family members.

Based on the current data, prophylactic hysterectomy is not first line treatment, but may be an option depending on a patients request and family history. It is worth noticing that an increased colonoscopy complication rate has been suggested for women previously undergoing pelvic surgery including hysterectomy, which could be an argument against this type of procedure (Shah et al., 2007).

8. Colorectal cancer

It is reported in two studies that more than 90% of patients with Cowden Syndrome and an average age of 35 or 48, respectively, have gastrointestinal polyps confirmed by colonoscopy (Heald et al., 2010) (Stanich et al., 2011). Hamartomas are most frequent, although, hyperplastic polyps, ganglioneuromas, adenomas and inflammatory polyps as well as leiomyomas, lipomas and lymphoid polyps are also seen (Heald et al., 2010) (Trufant et al., 2012) (Levi et al., 2011).

Historically, this characteristic polyposis tendency in Cowden Syndrome patients was not interpreted as an increased risk of colorectal malignancy (Schreibman et al., 2005).

However, recently, several groups have documented an increased risk of colorectal cancer at a young age in Cowden Syndrome patients. Stanich et al. showed a mean age of 47 at diagnosis, Heald et al. a mean age of 44 at the time of colorectal cancer diagnosis in patients with a clinical diagnosis while Niewenhuis et al. reported a mean age of 58 years in patients with a pathogenic *PTEN* variant (Nieuwenhuis et al., 2012) (Stanich et al., 2014) (Heald et al., 2010). These data are highly dependent on the age of the patients studied. The youngest Cowden Syndrome patient reported with colorectal cancer was 28 years old (Kersseboom et al., 2012).

The life time risk for colorectal cancer is estimated to be 9–16% among patients with Cowden syndrome (Stanich et al., 2014) (Tan et al., 2012) (Riegert-Johnson et al., 2010), however, it is uncertain whether the malignancy arises from adenomas or hamartomas. These risk estimates are 2–3 times higher compared to the general population (Danckert et al., 2019c). Another study, evaluating colorectal cancer risk in Cowden Syndrome patients did not reveal a significantly increased risk (Bubien et al., 2013). However, this study was limited by the small size of the patient cohort. Whether the risk estimates cited are accurate remains to be elucidated.

To date, only limited literature is available on upper gastrointestinal malignancy. Some studies have observed multiple hamartomatous polyps in the stomach, duodenum and small bowel with histology including hamartomas, hyperplastic polyps, ganglioneuromas, adenomas and inflammatory polyps (Heald et al., 2010) (Schreibman et al., 2005) (McGarrity et al., 2003). To our knowledge, only three reports of gastric cancer in Cowden Syndrome patients were published, and all the patients were above 60 years old (Schreibman et al., 2005) (Al-Thihli et al., 2009) (Heald et al., 2010). A well documented risk estimate remains to be established. Interestingly, for those patients undergoing gastroscopy for any reason, a greater proportion of glycogenic acanthosis was identified compared to the general population, although we still need a pathophysiologic explanation for this phenomenon (Heald et al., 2010).

In conclusion, the majority of patients with Cowden Syndrome have multiple polyps throughout the gastrointestinal tract with different histological presentations, and there seems to be a well-documented moderately increased risk of *lower* gastrointestinal malignancy. NCCN recommends colonoscopy starting from the age of 35 unless symptoms are present earlier. Colonoscopy should be performed every five years, or more frequent if the patient is symptomatic or polyps are present (NCCN, 2019). If a close relative is diagnosed with colorectal cancer before the age of 40, colonoscopy should be initiated 5–10 years prior to the age of diagnosis of the affected family member.

Colectomy due to polyps should rely on a clinical assessment.

Given the current knowledge, we propose surveillance with colonoscopy from the age of 35 and repeated every five years. An alternative regimen should be initiated earlier if polyps are found or the patient is symptomatic; presenting with bleeding, diarrhea, constipation, weight loss, pain or tiredness.

We do not recommend screening with gastroscopy.

9. Melanoma

Multiple trichilemmomas, oral papilloma and acral keratosis are characteristic and frequent findings in patients with pathogenic germline *PTEN* variants (Lope et al., 2017).

Recently, an increased estimated lifetime risk for melanoma of 6% has been suggested. Furthermore, the literature reports two cases of malignant melanoma in Cowden Syndrome patients at a very young age of only three and six years, respectively (Bubien et al., 2013) (Tan et al., 2012).

It is speculated whether dermatologic surveillance should be more

progressive (Pilarski, 2009). The current guideline from NCCN recommends dermatologic surveillance if needed, without specifying the criteria.

Because of potential socially disabling benign skin manifestations in Cowden Syndrome and the increased risk of malignant melanoma, we propose dermatological examination at the time of diagnosis and repeatedly if needed, based on an individual assessment at the Department of Dermatology.

10. Non-malignant manifestations

Macrocephaly is a head circumference defined as > 2 SD and is evident in the majority of Cowden Syndrome patients with deleterious variants in *PTEN* (Pilarski et al., 2011). Furthermore, associations have been suggested to developmental delay, autism spectrum disorder and epilepsy, although more studies are needed to fully elucidate the neurodevelopmental sequelae of Cowden Syndrome (Tilot et al., 2015) (Butler, 2005).

Hemangiomas and arteriovenous malformations are seen at increased frequencies in Cowden Syndrome patients (Hanssen and Fryns, 1995) (Turnbull, 2005). The arteriovenous malformations can present with severe pain and swelling, and most often be localized to the lower extremity. They may carry significant morbidity and mortality and management can be difficult, as they often involve the muscles and typically surround neurovascular structures (Kurek et al., 2012).

Additional dermatologic findings in Cowden Syndrome are: Papillomas, neuromas, acral keratosis, penile pigmentation, lipomas and fibromas (Pilarski et al., 2013).

A number of case reports have described meningiomas in Cowden Syndrome patients (Lok et al., 2005).

For the majority of the mentioned characteristics more data are needed to fully understand the risk and consequences of these manifestations in Cowden Syndrome.

Thus, we propose that adults undergo physical examination and start cancer surveillance from the time of diagnosis. In addition, it should be considered whether the patient has any sign of neurological or cognitive sequelae, which could indicate benefits of comprehensive neurological and/or neurodevelopmental examinations.

11. Genetic counseling

All patients with a suspected or confirmed diagnosis of Cowden Syndrome should be referred for genetic testing and counseling. The main purpose is to identify family members at risk.

12. General reflections

Our group reviewed the literature to ensure a minimum of biased trials and reviews, as well as including a high number of papers to minimize the risk of subjective results. A significant ascertainment bias needs to be addressed though. Three of our main references Tan et al., Bubien et al. and Niewenhuis et al. all used the same methodology. They all included patients with identified *PTEN* mutations and then estimated life time risks. This will typically lead to overestimates of life time cancer risk estimates because the patients which are most likely to undergo *PTEN* testing are those with one or multiple cancers. Currently, we are not in a position to more specifically determine life time risk estimates of cancer in Cowden Syndrome and therefore we must base our work on the current literature. However, it is important to address the biases, Table 2.

In our assessments of risk estimates and surveillance we used the age related penetrance curves from Tan et al. to estimate when initiation would be appropriate depending on the estimated risk.

Interestingly, looking at the age-related penetrance curves by Tan et al., the risk of renal cell cancer is 34%, but according to NCCNs guidelines ultrasound is only to be considered. The same applies to endometrial cancer, where a risk of 30% at age 60 years is reported, but the management guidelines again only recommends to consider ultrasound starting at age 30–35. This illustrates the importance of assessing when a risk estimate is high enough and at what age does the risk starts to increase.

Our proposal is based on the current data in the field. Longitudinal follow up of the patients will either validate the current knowledge or bring new insights which may change the recommendations. Furthermore, additional manifestations associated with Cowden Syndrome may be identified. In recent years an increasing number of people are being genetically screened. In case of the hypothesis about an underestimation of the prevalence of Cowden Syndrome being verified, more knowledge will be gained through the increasing number of diagnosed patients.

13. Cowden Syndrome in children

The age at which surveillance should be initiated has been somewhat controversial (Schreibman et al., 2005) (Heald et al., 2015).

Due to the above mentioned, non-malignant manifestations of Cowden Syndrome, we recommend that children undergo a physical examination at the time of diagnosis along with a thoroughly neurological and cognitive examination under the auspices of the Department of Pediatrics, as it is currently recommended in the Danish guidelines. It is essential that cognitive impairments and neurological symptoms in children are detected and managed optimally and instantaneously, with academic as well as social support and potential medical treatment. Consequently, follow up should be considered even in asymptomatic patients.

Concerning thyroid cancer, the youngest reported patient was 7 years and the NCCN recommends thyroid examination starting at the time of Cowden Syndrome diagnosis (NCCN, 2019) (Smith et al., 2011). Schultz et al. proposes a modification of the NCCN guidelines and suggests that thyroid examination should be initiated at age 7 due to the age of the youngest reported case and the indolent nature of papillary thyroid cancers. Surveillance should be repeated every 2 years (Schultz et al., 2017).

It is estimated by Tan et al. that five percent of patients with a *PTEN* mutation or Cowden Syndrome will develop thyroid cancer before the 20th year of life and according to age-related penetrance curves, risk for thyroid cancer begins at birth and continues lifelong (Tan et al., 2012). These estimates should be taken with reservations due to the previously mentioned ascertainment biases.

We propose that thyroid cancer surveillance should start at the time of diagnosis, but not before 15 years, as previously argued. From the age of 18, annually.

Cancer surveillance for other cancer types should follow the above proposed guidelines, given that other Cowden Syndrome related cancers are very rarely reported in children (Tan et al., 2012) (Smpokou et al., 2015). If a child presents with stomach pain, gastrointestinal bleeding, changed bowel pattern, a gastrointestinal endoscopy should be considered.

14. Conclusions

Cowden Syndrome is a complex cancer predisposition syndrome with a varied presentation. Cancer risk for several cancer subtypes are in numerous studies demonstrated to be elevated compared to the background population. Hence, once diagnosed with a pathogenic *PTEN* variant optimal surveillance for early cancer detection is crucial to ensure optimal survival and treatment options for the patients.

We aimed at optimizing the management guidelines for Cowden Syndrome patients based on risk estimates from the current literature for the well documented cancer subtypes associated with Cowden Syndrome.

Based on the included literature, we propose a surveillance program

Table 3
Surveillance recommendations as specified in the text, based on reported risk estimates.

Surveillance	Risk estimates	References	Recommendations
Physical examination	*N/A*		Physical, neurological and cognitive examination at the time of diagnosis. Consider follow up depending on patient symptoms and age
Breast	25–85%	(Tan et al., 2012) (Bubien et al., 2013) (Nieuwenhuis et al., 2014) (Starink' et al., 1986) (Shaco-Levy et al., 2017)	Annual clinical mammography starting at age 30. Consider MRI
Thyroid	14–35%	(Tan et al., 2012) (Milas et al., 2012) (Bubien et al., 2013) (Shaco-Levy et al., 2017)	Baseline ultrasound and clinical examination at age 15, from the age of 18, annually
Endometrial	19–29%	(Tan et al., 2012) (Riegert-Johnson et al., 2010) (Shaco-Levy et al., 2017)	Annual transvaginal ultrasound starting at age 30–35. Consider endometrial biopsy
Renal cell	17–34%	(Tan et al., 2012) (Shuch et al., 2013)	US or MRI of the kidneys every second year starting at age 40
Colon	9–16%	(Tan et al., 2012) (Heald et al., 2010) (Stanich et al., 2011) (Riegert-Johnson et al., 2010)	Colonoscopy every 5 years starting at age 35
Melanoma	6%	(Tan et al., 2012) (Bubien et al., 2013) (Shaco-Levy et al., 2017)	Dermatologic evaluation at the time of diagnosis and repeated based on individual assessment

as shown in Table 3. Indeed, it is valuable if a specialist will take the role as coordinator and contact person for the patient. We propose that such a person should be a specialist with a multidisciplinary approach to patients with rare diseases.

Compared to the previous guidelines, the current guidelines differ at some points due to new knowledge. We now recommend dermatological examination at baseline, and hereafter only individual assessments by a dermatologist, yearly ultrasound of the thyroid as earlier recommended but with a baseline scan at 15 years, ultrasound of the kidneys from the age of 40 and afterwards every second year independent of the family history. Colonoscopy every five years from the age of 35, instead of postponing the surveillance to the age of 50 if the baseline colonoscopy at 35 years is normal.

Endorsement

This work regarding colorectal cancer is endorsed by Niels Qvist, Department of Surgery A, Odense University Hospital, Odense, Denmark.

Proofreading

We thank Cecilie Abildgaard for proofreading.

Disclosures

The authors declare that they have no competing interests.

Funding

The corresponding author declares that there is no funding.

Authors' contributions

MPS did the main writing of the manuscript and a main part of the reference reading and work.

ABS was a major contributor in writing the manuscript.

AMJ was a contributor to the gastrointestinal section as well as revising it critically.

EE was a contributor to the thyroid section and to the overall proofreading of the manuscript.

KS was the main source of the idea to the project, was a major contributor in writing the manuscript as well as proofreading.

All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We would like to thank Niels Qvist, Department of Surgery A, Odense University Hospital, Odense, Denmark for endorsing the colorectal cancer section of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmg.2020.103873.

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