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CDC73 Mutations:

CDC73-related conditions include familial isolated hyperparathyroidism (FIHP), parathyroid carcinoma, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome.[1,2] Not everyone with a *CDC73* mutation will manifest symptoms, but up to 90% will develop a *CDC73*-related condition.

FIHP and hereditary parathyroid carcinoma do no involved other organs. However, HPT-JT is typically a multi-system neoplastic condition. Features include primary hyperparathyroidism due to parathyroid adenoma or carcinoma, ossifying fibroma(s) of the maxilla and/or mandible, renal lesions including cysts, hamartomas, and possibly Wilms tumor. [2]

In HPT-JT, the onset of primary hyperparathyroidism (PHPT) typically occurs in adolescence or early adulthood; 95% of cases will develop PHPT.[3,4]

- The risk of parathyroid carcinoma is 10-15%.[3]
- Approximately 20% of affected individuals develop renal cysts, hamartomas, and possibly Wilms tumor; however, the lifetime risk of kidney cancer is currently unclear.[3]
- The risks of ossifying jaw fibromas is 30-40%.[3]
- Benign and malignant uterine tumors appear to be common in women with HPT-JT syndrome.[5]

Management Recommendations

There are no established screening or surveillance guidelines for individuals with a pathogenic *CDC73* variant, but the following have been suggested to establish the extent of disease in an individual diagnosed with a *CDC73*-related disorder.[3,4]

- Evaluation for primary hyperparathyroidism: measurement of intact parathyroid hormone and serum calcium concentration
- Baseline bone density of the lumbar spine, hips, and distal radius by dual-energy x-ray absorptiometry (DXA) and 24-hour urine collection for calcium in individuals with evidence of primary hyperparathyroidism
- Evaluation for jaw tumors: panoramic jaw x-ray with neck shielding
- Evaluation for renal lesions: renal ultrasound examination preferred; CT and/or MRI as clinically indicated
- Evaluation for uterine tumors in women starting at reproductive age: pelvic examination as part of routine gynecologic care; pelvic ultrasound examination in any woman with a menstrual disorder with further imaging studies (CT and/or MRI) as clinically indicated

The following surveillance guidelines have been proposed:[3]

- Annual serum calcium, iPTH, and 25-(OH) vitamin D (to evaluate for possible coexisting vitamin D deficiency as a cause of elevated iPTH levels or unexpectedly "normal" calcium concentrations), starting at age 5.
- In patients with a history of parathyroid carcinoma who develop a rise in calcium levels, consider the possibility of a new primary parathyroid tumor in addition to recurrence/progression of malignant disease.
- Consider periodic parathyroid ultrasound examination for the detection of non-functioning parathyroid carcinoma, which has developed on rare occasion.
- Obtain panoramic x-ray dental imaging with neck shielding at least every five years. Dental providers should be notified of the presence of a *CDC73*-related disorder and the need for monitoring for osseous fibromas of the maxilla and mandible.
- Monitor for kidney lesions by renal ultrasound examination at least every five years, starting at the age of diagnosis.
    - Serum creatinine concentrations should be monitored in those individuals with renal cysts.
    - Individuals with solid lesions should be referred for appropriate subspecialty care.

- Starting at reproductive age, women with a *CDC73*-related disorder should undergo regular gynecologic care (including pelvic examination).
    - Care providers in obstetrics and gynecology should be notified of the risk of uterine tumors
    - Pelvic ultrasound examination should be obtained for any woman with a menstrual disorder (particularly abnormal uterine bleeding or menorrhagia), with further imaging studies (CT or MRI) as clinically indicated.

In addition, it is recommended that individuals with *CDC73*-related conditions avoid dehydration, radiation exposure, and biopsy of extra-thyroid neck tissue, which may increase the risk of seeding a possible parathyroid carcinoma.[3]

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *CDC73* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.findageneticcounselor.com to find genetic services near them.

References*:*

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