Last Updated March 2020

POLD1 **Mutations**

A mutation in the *POLD1* gene is associated with a predisposition to hereditary polyposis (the growth of many polyps in the colon) and colorectal cancer. The proposed name for this condition is Polymerase Proofreading-Associated Polyposis Syndrome (PPAP).[1] Individuals with a *POLD1* mutation typically present before the age of 60 with colorectal cancer (often microsatellite stable) and fewer than 100 adenomas. The clinical spectrum ranges from large polyps (>2 cm in diameter) to multiple adenomas.[1-3]

A mutation in the *POLD1* gene is also associated with mandibular hypoplasia, deafness, progeroid (early aging) features and lipodystrophy (MDPL) syndrome. MDPL is a rare, systemic disorder that is characterized by the loss of subcutaneous fat, distinctive facial features, and metabolic abnormalities including insulin resistance and diabetes. Sensorineural hearing loss typically occurs late in the first or second decades of life.[4,5]

Cancer Risks and Management Recommendations

Below are general guidelines for management based on National Comprehensive Cancer Network (NCCN) practice guidelines, version 3.2019.

Cancer Type	***POLD1*** **Mutation Carrier Cancer Risks**[2,3,6]	**General Population Lifetime Cancer Risks**	**Surveillance/Management Recommendations**[7]
Colorectal	82-90%	4.5%	*Surveillance* • Colonoscopy every 1-2 years starting at age 25-30 years, repeating every 2-3 years if no polyps are found • If polyps are found, colonoscopy every 1-2 years with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy • Surgical evaluation should be considered if appropriate.

Uterine/ endometrial	Increased (lifetime risk unknown)	2.7%	*Surveillance* • No clear evidence to support screening for uterine cancer in women with *POLD1* mutations. • Screening via endometrial biopsy every 1-2 years can be considered. Transvaginal ultrasound may be considered at clinician's discretion. *Surgery* • Hysterectomy is a risk-reducing option that can be considered. • Timing should be individualized based on whether childbearing is complete, comorbidities, family history and gene mutation. *Chemoprevention* • In the general population, oral contraceptive use has been associated with a decreased risk of uterine cancer by 50%.

Other cancer risks: Some studies have suggested that there may be an increased risk for cancers of the ovary, pancreas, brain, small intestine, and breast in people with a *POLD1* mutation.[6,8] However, further studies are needed to better understand these risks. At this time there is not enough evidence to support increased screening for these cancers based on a *POLD1* mutation alone. An individual's personal and family history should be considered in developing an appropriate surveillance plan.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to inherit the familial *POLD1* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to inherit 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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