There are more rare genetic cancer predisposition syndromes that can have other clinical manifestations. The National Comprehensive Cancer Network (NCCN v 1.2018) recommends further evaluation for the following:

PEUTZ-JEGHERS

Any individual with a personal or family history of any of the following should be offered further evaluation for Peutz-Jeghers syndrome:

- dermatologic manifestations (trichilemmomas, palmoplantar keratoses, oral mucosal papillomatosis, cutaneous facial papules)
- macrocephaly
- hamartomatous polyps of the GI tract

LI FRAUMENI

Any individual with a personal or family history of any of the following should be offered further evaluation for Li Frameni syndrome:

- From a family with a known TP53 gene mutation
- Meeting Classic Li-Fraumeni syndrome criteria:
    - Any individual diagnosed with a sarcoma before age 45, AND
    - A first-degree relative diagnosed with cancer before age 45, AND
    - An additional first- or second-degree relative in the same lineage with cancer diagnosed before age 45, or diagnosed with sarcoma at any age
- Meeting Chompret criteria:
    - Any individual with a tumor from LFS tumor (soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma) before age 46 AND at least one first- or second-degree relative with a LFS tumor before the age of 56 (both cannot be breast cancer), or with multiple primaries at any age

OR

    - Any individual with multiple tumors (except multiple breast tumors), two of which are LFS tumors, with the initial cancer being diagnosed before the age of

46

OR

- Any individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype at any age of onset regardless of family history

OR

- Breast cancer diagnosed before age 31

COWDEN SYNDROME/PTEN HAMARTOMA TUMOR SYNDROME

In order to more clearly understand the criteria for referral, it is helpful to be familiar with the 'Major' and 'Minor' criteria for Cowden syndrome:

- **MAJOR CRITERIA**
  - Breast cancer
  - Endometrial cancer
  - Follicular thyroid cancer
  - Multiple GI hamartomas or ganglioneuromas
  - Macrocephaly/Megalocephaly (above the 97th percentile; 58cm in women and 60cm in men)
  - Macular pigmentation of the glans penis
  - Mucocutaneous lesions
    - One biopsy-proven trichilemmoma
    - Multiple palmoplantar keratoses
    - Multifocal or extensive oral mucosal papillomatosis
    - Multiple cutaneous facial papules
- **MINOR CRITERIA**
  - Autism spectrum disorder

    - Colon cancer
    - Three or more esophageal glycogenic acanthoses
    - Lipomas
    - Intellectual disability (IQ of 75 or less)
    - Papillary or follicular variant of papillary thyroid cancer
    - Thyroid structural lesions (adenoma, nodules, goiter, etc)
    - Renal cell carcinoma
    - Single GI hamartoma or ganglioneuroma
    - Testicular lipomatosis
    - Vascular anomalies (including multiple intracranial developmental venous anomalies)

Any individual with any of the following should be offered further evaluation for Cowden syndrome/PTEN hamartoma tumor syndrome:

- From a family with a known PTEN gene mutation
- Personal history of Bannayan-Riley-Ruvalcaba syndrome
- Meeting clinical diagnostic criteria
    - Three or more major criteria (one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas), OR
    - Two major and three minor criteria
- NOT meeting clinical diagnostic criteria, but with a personal history of:
    - Adult Lhermitte-Duclos disease (cerebellar tumors), OR
    - Autism spectrum disorder and macrocephaly, OR
    - Two or more biopsy-proven trichilemmomas, OR
    - Two or more major criteria (one must be macrocephaly), OR
    - Three major criteria (without macrocephaly), OR
    - One major and three or more minor criteria
    - Four or more minor criteria
- From a family with a relative who has a clinical diagnosis of Cowden syndrome (but genetic testing has not been done), and the individual has any one major or two minor criterion