Stage I: Binning Dashboard

Incidental Findings in Adults

Non-diagnostic, excludes newborn screening & prenatal testing/screening

GENE/GENE PANEL: *PTEN*
DISORDER: PTEN Hamartoma Tumor Syndrome – Cowden syndrome
HGNC ID: 9588
OMIM ID: 158350

ACTIONABILITY

1. **Is there a qualifying resource, such as a practice guideline or systematic review, for the genetic condition?**

☒ **YES** ☐ **NO**

2. **Does the practice guideline or systematic review indicate that the result is actionable in one or more of the following ways?**

Yes	No	
☒	☐	Patient Management
☒	☐	Surveillance or Screening
☒	☐	Family Management
☒	☐	Circumstances to Avoid

☒ **YES (≥ 1 of above)** ☐ **NO**

3. **Is the result actionable in an undiagnosed adult with the genetic condition?**

☒ **YES** ☐ **NO**

PENETRANCE

4. **Is there at least one known pathogenic variant with at least moderate penetrance (≥40%) or moderate relative risk (≥2) in any population?**

☒ **YES** ☐ **NO**

SIGNIFICANCE/BURDEN OF DISEASE

5. **Is this condition an important health problem?**

☒ **YES** ☐ **NO**

NEXT STEPS

6. **Are Actionability (Q2-3), Penetrance (Q4), and Significance (Q5) all "YES"?**

☒ **YES (Proceed to Stage II)**

☐ **NO (Consult Actionability Working Group)**

- ☐ **Exception granted, proceed to Stage II**
- ☐ **Exception not granted, STOP**

Stage II: Binning Summary

Incidental Findings in Adults

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GENE/GENE PANEL: *PTEN*		**DISORDER:** PTEN Hamartoma Tumor Syndrome – Cowden syndrome	
Topic		**Narrative Description of Evidence**	**Ref**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Prevalence of the genetic disorder		The true prevalence of Cowden syndrome (CS) is unknown.	[1-6]
Signif/Burden of Condition	**Clinical Features**	CS is part of the *PTEN* hamartoma tumor syndrome (PHTS) spectrum. CS is a cancer syndrome associated with a high risk of hamartomas and/or cancerous lesions in various organs and tissues, including the skin, mucous membranes, breast, thyroid, endometrium, and brain. Macrocephaly is a common manifestation.	[1-6]
		Hamartomatous polyps of the colon and other intestines also occur.	[1;3;5;6]
		Renal cell carcinoma and malignant melanoma may be minor component neoplasias of CS.	[1;3;4;6]
	Natural History	More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata, as well as acral and plantar keratoses.	[1;3]
		The average age of breast cancer diagnosis is between 38 and 46 years.	[1;3]
		The median age of epithelial thyroid cancer onset is 37 years. Elevated risk for endometrial cancer, colorectal cancer, and renal cell carcinoma starts in the late 30s and early 40s.	[3]
2. How effective are interventions for preventing the harm?			
Patient Management		Information on the effectiveness of the patient management recommendations below was not available.	
		At diagnosis: individuals should undergo a physical examination, paying particular attention to skin, mucous membranes, thyroid, and breasts; urinalysis; and medical genetics consultation. Individuals diagnosed after ages 35 and 40 should undergo colonoscopy and renal imaging, respectively. Women diagnosed after age 30 should undergo breast screening and transvaginal ultrasound. **(Tier 4)**	[3]
		Dermatologic management may be indicated for some patients. **(Tier 2)**	[1]
		Risk-reduction mastectomy and hysterectomy should be discussed on a case-by-case basis. **(Tier 2)**	[1]
		CS patients should be educated about the signs and symptoms of cancer. **(Tier 2)**	[1]
Surveillance		Information on the effectiveness of the surveillance recommendations below was not available.	
		CS patients should undergo annual comprehensive examinations. **(Tier 2)**	[1]
		Women should be breast aware starting at age 18, including periodic, consistent breast self-exam. Clinical breast exam, every 6-12 months, should begin at age 25, or 5-10 years before the earliest known breast cancer in the family. **(Tier 2)**	[1]
		Women should undergo annual mammography and breast MRI screening starting at age 30-35 or individualized based on earliest age of onset in the family. **(Tier 2)**	[1;7]
		Women should consider annual random endometrial biopsies and/or ultrasound beginning at age 30-35. **(Tier 2)**	[1]
		Individuals with CS should receive annual thyroid ultrasounds starting at age 18 or 5-10 years before the earliest known thyroid cancer in the family, whichever is earlier. **(Tier 2)**	[1]
		Individuals with CS should undergo colonoscopy, starting at age 35, then every 5 years, or more	

Stage II: Binning Summary

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	frequently if patient is symptomatic or polyps are found. **(Tier 2)** Consider renal ultrasound starting at age 40, then every 1-2 years. **(Tier 2)**	[1] [1]
Family Management	Genetic counseling and consideration of genetic testing is recommended for at-risk relatives. An individual with a known deleterious *PTEN* mutation in a close family member who does not undergo gene testing should be followed according to the same guidelines as a carrier of a *PTEN* mutation. **(Tier 2)**	[1]
Circumstances to Avoid	Because of the propensity for rapid tissue regrowth, it is recommended that cutaneous lesions be excised only if malignancy is suspected or symptoms are significant. **(Tier 4)**	[3]

Description of sources of evidence:

Tier 1: Evidence from a systematic review, or a meta-analysis or clinical practice guideline clearly based on a systematic review
Tier 2: Evidence from clinical practice guidelines or broad-based expert consensus with non-systematic evidence review
Tier 3: Evidence from another source with non-systematic review of evidence with primary literature cited
Tier 4: Evidence from another source with non-systematic review of evidence with no citations to primary data sources
Tier 5: Evidence from a non-systematically identified source

GENE/GENE PANEL: *PTEN*	**DISORDER:** PTEN Hamartoma Tumor Syndrome – Cowden syndrome	
Topic	**Narrative Description of Evidence**	**Ref**
3. What is the chance that this threat will materialize?		
Mode of Inheritance	Autosomal dominant	
Prevalence of Genetic Mutations	Information on the prevalence of PTEN mutations was not available.	
Penetrance **OR** **Relative Risk** (include high risk racial or ethnic subgroups)	More than 90% of individuals with CS have some clinical manifestation of the disorder by the late 20s. By the third decade, 99% of affected individuals develop the mucocutaneous stigmata. **(Tier 3)** Among individuals meeting the diagnostic criteria for CS, the cumulative lifetime risk of any cancer is 89%. **(Tier 3)** The lifetime risk of breast cancer for females with a *PTEN* pathogenic variant is 77-85%, with 50% penetrance by age 50. **(Tier 3)** Lifetime risk of epithelial thyroid cancer ranges from 21-38%. Lifetime risk of endometrial cancer ranges from 19-28%. Lifetime risk of renal cell cancer ranges from 32-34%. Lifetime risk of colorectal cancer ranges from 9-16%. **(Tier 3)**	[1;3] [1] [3;6] [1;3;6]
Expressivity	The high variability in disease expression is highlighted by the fact that clinical diagnosis in an individual is based on three of eight possible major diagnostic criteria, or two major criteria and three of eleven possible minor criteria. **(Tier 2)**	[1]
4. What is the nature of the intervention?		
Nature of Intervention	Management of CS includes regular invasive and non-invasive screening tests and the possible recommendation of prophylactic organ removal for affected women.	
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?		
Chance to Escape Clinical Detection	Given the age of development of cancers in CS patients, general population screening would not allow for prophylactic measures to be taken. The increased cancer surveillance in this population will allow detection of tumors at the earliest, most treatable stages.	[3]

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Final Consensus Scores						
Gene(s)	**Outcome/intervention pair**	**Severity**	**Likelihood**	**Effectiveness**	**Nature of the Intervention**	**Total Score**
PTEN	Breast cancer/Surveillance	2	3C	2B	3	10CB
	Thyroid cancer/Surveillance	2	2C	2B	3	9CB

To see the scoring key, please go to: https://clinicalgenome.org/working-groups/actionability/projects-initiatives/actionability-evidence-based-summaries/.

Date of Search (MM.DD.YYYY): 07.11.2014

References

[1] National Comprehensive Cancer Network. Genetic/Familial High-Risk Assessment: Breast and Ovarian. 2014 Feb 28.

[2] Hall JE, Abdollahian DJ, Sinard RJ. Thyroid disease associated with Cowden syndrome: A meta-analysis. Head Neck 2013 Aug;35(8):1189-94.

[3] Eng C. GeneReview: PTEN Hamartoma Tumor Syndrome (PHTS). 1-23-2014. 7-10-2014.
Ref Type: Online Source

[4] Eng C. Will the real Cowden syndrome please stand up: revised diagnostic criteria. J Med Genet 2000 Nov;37(11):828-30.

[5] McKusick V, Hamosh A. OMIM: Cowden Syndrome 1. 12-20-2013. 7-11-2014.
Ref Type: Online Source

[6] Eng C. Orphanet: PTEN hemartoma tumor syndrome. 7-1-2013. 7-11-2014.
Ref Type: Online Source

[7] Alberta Health Service. Magnetic Resonance Imaging for Breast Cancer Screening, Pre-Operative Assessment, and Follow-up. 2012 Jan 1.