Stage I: Binning Dashboard

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: **CONDITION:**

ACTIONABILITY

1. **Is there a practice guideline or systematic review for the genetic condition?**

   ☐ **YES** ☐ **NO (STOP)**

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 (STOP)**

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

   ☐ **YES** ☐ **NO (STOP)**

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 (STOP)**

SIGNIFICANCE/BURDEN OF DISEASE

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

   ☐ **YES** ☐ **NO (STOP)**

ACTIONABILITY, PENETRANCE, AND SIGNIFICANCE/BURDEN Must *ALL* be "YES" to continue

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL:	**CONDITION:**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Disease Incidence			☐ Known ☐ Unknown
Disease prevalence			☐ Known ☐ Unknown
Clinical Features (Signs/symptoms)			☐ Known ☐ Unknown
Natural History (Important subgroups & survival/recovery)			☐ Known ☐ Unknown
Significance/Burden of Condition			☐ Known ☐ Unknown
2. How effective are interventions for preventing the harm?			
Patient Management	**(Tier X)**		☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Surveillance	**(Tier X)**		☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Family management	**(Tier X)**		☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Circumstances to Avoid	**(Tier X)**		☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL:	**CONDITION:**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
3. What is the chance that this threat will materialize?			
Prevalence	**(Tier X)**		☐ Known ☐ Unknown
Penetrance **OR**	**(Tier X)**		☐ High (>60%) ☐ Moderate (40-60%) ☐ Low (<40%) ☐ Unknown
Relative Risk (include any high risk racial or ethnic subgroups)	**(Tier X)**		☐ High (>3) ☐ Moderate (2-3) ☐ Low (<2) ☐ Unknown
Expressivity	**(Tier X)**		☐ Known ☐ Unknown
4. How acceptable are the interventions in terms of the burdens or risks placed on the individual?			
Acceptability of Intervention	**(Tier X)**		☐ Very Acceptable ☐ Mildly Acceptable ☐ Risky or problematic
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?			
Chance to escape clinical detection in Adults	**(Tier X)**		☐ Often ☐ Sometimes ☐ Rarely ☐ Unknown

AAT Summary

Recommendation:

Rationale:

References

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Stage I: Binning Dashboard

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: APC | **CONDITION: Familial Adenomatous Polyposis (FAP)**

ACTIONABILITY

1. **Is there a practice guideline or systematic review for the genetic condition?**

   ☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

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

   ☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

SIGNIFICANCE/BURDEN OF DISEASE

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

   ☒ **YES** ☐ **NO (STOP)**

ACTIONABILITY, PENETRANCE, AND SIGNIFICANCE/BURDEN Must *ALL* be "YES" to continue

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE: APC	**CONDITION: Familial Adenomatous Polyposis (FAP)**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Disease Incidence	Age adjusted incidence rate for colorectal cancer (CRC) is 46.3 per 100,000 men and women per year. It is estimated that 143,460 men and women will be diagnosed with and 51,690 will die of CRC in 2012. FAP accounts for <1% of the annual CRC burden	1,4	☒ Known ☐ Unknown
Disease prevalence	Based on rates from 2007-2009, 1 in 20 men and women born today will be diagnosed with CRC during their lifetime. On January 1, 2009, there were about 1,140,000 men & women alive with a history of CRC.	1,4	☒ Known ☐ Unknown
Clinical Features (Signs/symptoms)	Clinical FAP is classically diagnosed as having > 100 adenomas. In virtually all patients, at least one of these adenomas will eventually progress to colon cancer. Extracolonic features include increased risk of desmoid tumors and duodenal cancer.	8	☒ Known ☐ Unknown
Natural History (Important subgroups & survival/recovery)	In the absence of surgical intervention, virtually all individuals with FAP will develop colon cancer with an average age of onset of 40-50 years of age, with some individuals developing cancer as young as 12-15 years of age.	8	☒ Known ☐ Unknown
Significance/Burden of Condition	The 5-year relative survival (compared to a general population) was 90% for localized, 70% for regional, and 12% for distant CRC; overall across all disease stages 5-year relative survival was 64.3%.	1,2,4	☒ Known ☐ Unknown
2. How effective are interventions for preventing the harm?			
Patient Management	Central registration and prophylactic colectomy or proctocolectomy performed when number of adenomas reaches 20 or 30, or become symptomatic has been shown to reduce overall and colon-cancer-related mortality in patients with FAP in at least 3 studies. **(Tier 2)** Removal of desmoid and duodenal tumors confers an additional benefit **(Tier 3)**. Some patients benefit from treatment with NSAIDs. **(Tier 3)**	4,8 1,8 1,8	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Surveillance	Pre-colectomy surveillance – sigmoidoscopy every 1-2 years starting at age 10-12 years has been shown to reduce FAP mortality. **(Tier 2)** Post-colectomy surveillance includes annual sigmoidoscopy in those with retained rectum, upper endoscopy every 1-3 years depending on polyp burden, annual thyroid examination, and annual abdominal examination plus possible imaging studies (CT or MRI) if family has a history of desmoid tumors (**Tier 2)**	4,8 4	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Family management	Early recognition may allow for timely intervention and improve final outcome; genetic testing is more cost effective than sigmoidoscopy in determining who in the family is affected.[16] Surveillance (described above) is recommended for individuals with a known APC mutation, individuals at risk for FAP who have not undergone molecular genetic testing, and individuals who are members of families in which molecular genetic testing did not identify a disease-causing mutation. **(Tier 3)**	1	☐ Highly Effective ☒ Somewhat Effective ☐ Not Effective ☐ Unknown
Circumstances to Avoid			☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☒ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE: APC	**CONDITION: Familial Adenomatous Polyposis (FAP)**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
3. What is the chance that this threat will materialize?			
Prevalence	Estimates range from 2 to 10 per 100,000, with 15 – 25% of cases resulting from a *de novo* mutation. **(Tier 2)**	1,8	☒ Known ☐ Unknown
Penetrance **OR**	Penetrance is virtually 100% for occurrence of colon cancer. **(Tier 2)**	1,2,3,4,8	☒ High (>60%) ☐ Moderate (40-60%) ☐ Low (<40%) ☐ Unknown
Relative Risk (include any high risk racial or ethnic subgroups)			☐ High (>3) ☐ Moderate (2-3) ☐ Low (<2) ☐ Unknown
Expressivity	Polyps begin to appear at variable ages, ranging from teens to sixties, with an average age of first polyps at 16. It has recently been reported that as many as 15% of patients with FAP display mosaicism. **(Tier 3)**	1,8	☒ Known ☐ Unknown
4. How acceptable are the interventions in terms of the burdens or risks placed on the individual?			
Acceptability of Intervention	Colectomy or proctocolectomy can result in hemorrhage, loss of fertility, sexual dysfunction, increased fecal frequency and urgency, incontinence, dietary restriction and post-surgical complications. 3-28% of patients require re-operation within 30 days. Some patients require an ostomy. **(Tier 2)**	1,4,8	☐ Very Acceptable ☐ Mildly Acceptable ☒ Risky or problematic
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?			
Chance to escape clinical detection in Adults	Colon cancers resulting from FAP are aggressive and the incidence of cancer is not 100% predictable from polyp burden or other available clinical features. Even with an annual sigmoidoscopy, it is possible for patients to progress from cancer-free to terminal cancer between screenings. **(Tier 3)**	8	☐ Often ☒ Sometimes ☐ Rarely ☐ Unknown

FAP Summary

Recommendation: Routinely report as a clinically actionable incidental finding.

Rationale: A significant disease burden is associated with FAP. Although there are risks associated with the interventions for FAP, these are outweighed by the potential benefits from surveillance and risk-reducing surgeries for the individual and their family members. This summary is limited to mutations consistent with classic FAP.

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

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Stage I: Binning Dashboard

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: SERPINA1 | **CONDITION: α1-antitrypsin (AAT) deficiency**

ACTIONABILITY

1. **Is there a practice guideline or systematic review for the genetic condition?**

   ☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

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

   ☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

SIGNIFICANCE/BURDEN OF DISEASE

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

   ☒ **YES** ☐ **NO (STOP)**

ACTIONABILITY, PENETRANCE, AND SIGNIFICANCE/BURDEN Must *ALL* be "YES" to continue

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: SERPINA1	**CONDITION: α1-antitrypsin (AAT) deficiency**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Disease Incidence	The death rates for COPD are 46.4 per 100,000 for US men and 34.2 per 100,000 in US women.	1	☒ Known ☐ Unknown
Disease prevalence	In 2009, 13.1 million U.S. adults > 18 years had COPD. AAT deficiency accounts for around 2% of cases of COPD. In Caucasians, the prevalence of AAT deficiency is 25 out of 10,000.	10 2 3	☒ Known ☐ Unknown
Clinical Features (Signs/symptoms)	Severe AAT deficiency is characterized by a reduced serum level of AAT, and increased risk for developing early-onset pulmonary emphysema, and by an accumulation of polymers of the AAT within the hepatocytes which might promote liver disease. COPD, specifically emphysema, is the most common clinical manifestation of AAT deficiency. The onset of disease in smokers is between 40-50 years. In non-smokers, the onset can be delayed to the sixth decade and is often associated with a normal life span. Cirrhosis and carcinoma of the liver affect about 30-40% of patients with AAT deficiency over the age of 50 years and are a significant cause of death in nonsmoking individuals with the PI ZZ phenotype.	4 5 5	☒ Known ☐ Unknown
Natural History (Important subgroups & survival/recovery)	In the US the highest risk for AAT deficiency is found in Whites. The severity of airflow obstruction in AAT deficiency, age at presentation of respiratory symptoms, and physiologically demonstrable airflow obstruction vary widely. Several studies report early death of individuals with AAT deficiency-associated lung disease. Cirrhosis of the liver occurs in 5-15% of AAT deficient adults with higher figures for the elderly, particular never-smokers who escape severe emphysema.	2 5	☒ Known ☐ Unknown
Significance/Burden of Condition	AAT deficiency increases risk for serious conditions including COPD, and cirrhosis and carcinoma of the liver.	5	☒ Known ☐ Unknown
2. How effective are interventions for preventing the harm?			
Patient Management	Influenza and pneumococcal vaccination is recommended. **(Tier 1)** Testing for hepatitis serology is recommended. **(Tier 1)** Regular exercise, good nutrition, and vitamin E therapy are predicted to help prevent damage to the lungs. **(Tier 4)**	5 5 6	☐ Highly Effective ☒ Somewhat Effective ☐ Not Effective ☐ Unknown
Surveillance	Surveillance for hepatocellular carcinoma is recommended in patients with AAT deficiency and cirrhosis. **(Tier 2)** Elderly patients with AAT deficiency who lack liver symptoms should have regular assessment of simple liver function tests. **(Tier 1)** Monitor patients with liver function tests & measurements. **(Tier 4)**	7 5 6	☐ Highly Effective ☒ Somewhat Effective ☐ Not Effective ☐ Unknown
Family management	Not applicable		
Circumstances to Avoid	Curtail cigarette smoking and eliminate environmental pollutants. Early cessation of smoking is particularly important in those with the homozygous phenotype. Minimize exposure to respiratory irritants such as second-hand tobacco smoke, dusts, and fumes. Avoid occupations where such exposure occurs frequently. **(Tier 1)** Patients should be urged to stop drinking alcohol. **(Tier 4)**	5 8	☐ Highly Effective ☒ Somewhat Effective ☐ Not Effective ☐ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: SERPINA1	CONDITION: α1-antitrypsin (AAT) deficiency		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
3. What is the chance that this threat will materialize?			
Prevalence	A meta-analysis of the US based studies estimated the following frequencies: • PI S allele: 3.31% • PI Z allele: 1.2% • PI SZ heterozygotes: 0.08% • PI ZZ homozygotes: 0.014% **(Tier 1)**	4	☒ Known ☐ Unknown
Penetrance **OR** **Relative Risk** (include any high risk racial or ethnic subgroups)	Penetrance of COPD is not properly known because many PI ZZ individuals are never identified. Screening studies in the US indicate that the prevalence of individuals with AAT deficiency is between 1 in 2, 857 and 1 in 5,097 which would expect 80,000 to 100,000 individuals with AAT (symptomatic and asymptomatic) in the US. Only 3,000-4,000 individuals have been diagnosed indicating that it undiagnosed or not manifested in a large proportion of the patients. **(Tier 1)**	5	☐ High (>60%) ☐ Moderate (40-60%) ☐ Low (<40%) ☒ Unknown
	In a meta-analysis of studies comparing COPD in PI SZ compound heterozygotes, a three-fold elevation in COPD risk due to the PI SZ genotype was found. **(Tier 1)** Homozygous PI ZZ confers a 20 times higher risk of chronic liver disease. **(Tier 1)**	9 5	☒ High (>3) ☐ Moderate (2-3) ☐ Low (<2) ☐ Unknown
Expressivity	There is considerable variation in the clinical manifestations produced by AAT deficiency, some patients have minimal or no symptoms and others develop severe emphysema at an early age. Smoking is the major factor in developing emphysema but some non-smokers develop airflow limitation in later life and this appears to be associated with a history of asthma or pneumonia. **(Tier 1)**	3	☐ Known ☒ Unknown
4. How acceptable are the interventions in terms of the burdens or risks placed on the individual?			
Acceptability of Intervention	Data not identified. However, harms would be limited to those associated with immunization and hepatocellular carcinoma screening.		☒ Very Acceptable ☐ Mildly Acceptable ☐ Risky or problematic
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?			
Chance to escape clinical detection in Adults	Symptomatic obstructive lung disease in AAT deficiency usual presents at a mean age between 32 and 41 years in individuals with a history of smoking. Considerable variability in the time of onset of symptoms has been described but symptoms rarely present before age 25 years. Although severe symptoms are most often seen in current or previous cigarette smokers, some smokers and many nonsmokers develop no symptoms at all.**(Tier 1)** Nonsmoking individuals with the homozygous Z phenotype have a remarkably delayed onset of symptoms and some have an almost normal lifespan.**(Tier 1)**	5 5	☐ Often ☒ Sometimes ☐ Rarely ☐ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

AAT Summary

Recommendation: Routinely report as a clinically actionable incidental finding.

Rationale: AAT deficiency can lead to very serious health conditions including COPD, cirrhosis and carcinoma of the liver. The penetrance is not well-understood, but based on prevalence estimates it may be significantly under-diagnosed or does not manifest in a large proportion of patients who carry a high risk genotype. Although the interventions are considered somewhat effective, a minority view was that the actions are not sufficiently different from recommendations for a general population (e.g., influenza vaccination, regular exercise, good nutrition, and smoking cessation), and the main benefit may be to motivate smoking cessation, although the effectiveness of using genetically identified risk information to promote this behavior change compared with other approaches is uncertain.

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Stage I: Binning Dashboard

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: HFE | **CONDITION: HFE-associated Hereditary Hemochromatosis (HFE-HH)**

ACTIONABILITY

1. **Is there a practice guideline or systematic review for the genetic condition?**

☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

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

☒ **YES** ☐ **NO (STOP)**

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 (STOP)**

SIGNIFICANCE/BURDEN OF DISEASE

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

☒ **YES** ☐ **NO (STOP)**

ACTIONABILITY, PENETRANCE, AND SIGNIFICANCE/BURDEN Must *ALL* be "YES" to continue

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: HFE	**CONDITION: HFE-associated hereditary hemochromatosis (HFE-HH)**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
1. What is the nature of the threat to health for an individual carrying a deleterious allele?			
Disease Incidence	About 80,000 hemochromatosis or hemochromatosis-compatible disease hospitalizations (2.3 per 100,000 residents) in the US from 1979-1997. Of 29 million deaths from 1979-1992 4,848 (0.017%) were consistent with hemochromatosis as the underlying cause. Age-adjusted mortality rates for hemochromatosis-consistent death increased from 1.2 per million (1979) to 1.8 per million (1992).	1	☒ Known ☐ Unknown
Disease prevalence	The prevalence of HH in the primary care population is estimated 0.18-0.59%.	2	☒ Known ☐ Unknown
Clinical Features (Signs/symptoms)	HH is characterized by excessive intestinal absorption of iron with progressive abnormal deposition in various organs, such as the liver, heart, pancreas, joints, and skin. Even in the absence of iron overload, iron accumulates when the liver is inflamed or cirrhosed. Cirrhosis is a late-stage disease development and has been reported to shorten life expectancy. *HFE*-HH is defined as C282Y homozygosity and increased body iron stores with or without clinical symptoms.	3 1 4	☒ Known ☐ Unknown
Natural History (Important subgroups & survival/recovery)	Clinically recognized HH is twice as common in males and occurs mostly in white populations. The condition has a long latent period with wide individual variation in expression. Iron accumulation and disease expression are modified by factors such as blood loss from menstruation or donation, alcohol intake, diet, and comorbid disease (e.g., viral hepatitis). Age of onset is delayed in females.	1	☒ Known ☐ Unknown
Significance/Burden of Condition	The pathophysiologic predisposition to dietary iron absorption may lead to the development of life-threatening complications of cirrhosis, hepatocellular carcinoma, diabetes, and heart disease.	5	☒ Known ☐ Unknown
2. How effective are interventions for preventing the harm?			
Patient Management	<u>Patients with increased iron stores</u> • Patients could be immunized against hepatitis A and B. **(Tier 1)** • Patients should be treated with phlebotomy. **(Tier 1)** • Liver biopsy offered to C282Y/C282Y patients with ferritin above 1000 ug/L, elevated AST, hepatomegaly, or age > 40 years. **(Tier 1)** • Liver biopsy to stage liver disease in compound heterozygotes if liver enzymes are elevated or if ferritin is >1000 ug/L. **(Tier 2)**	4 4 4 5	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Surveillance	Patients should enter surveillance programs for hepatocellular carcinoma. (**Tier 2)** <u>Asymptomatic individuals with no excess iron</u> • C282Y/C282Y- annual monitoring and treatment when ferritin rises above normal. **(Tier 1)** • C282Y/H63D- measure iron overload indices (transferrin saturation, ferritin) every 3 years. **(Tier 3)** • C282Y hetero- measure iron indices every 5 years. **(Tier 3)** • H63D/H63D- Consider regular monitoring of iron indices. **(Tier 3)** May prevent progression by donating blood regularly. **(Tier 4)**	8 4 6 6 6 7	☒ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☐ Unknown
Family management	Not applicable		
Circumstances to Avoid	During treatment for HH avoid vitamin C & iron supplements **(Tier 2)** Patients should avoid mineral supplements and uncooked seafood. Avoid alcohol consumption in those with hepatic involvement. **(Tier 4)**	5 9	☐ Highly Effective ☐ Somewhat Effective ☐ Not Effective ☒ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

GENE/GENE PANEL: HFE	**CONDITION: HFE-associated hereditary hemochromatosis (HFE-HH)**		
Topic	**Narrative Description of Evidence (Include Tier for Questions 2-5)**	**Ref**	**Judgment**
3. What is the chance that this threat will materialize?			
Prevalence	The frequency of the C282Y polymorphism is 6.2% in the general population. Therefore, homozygosity is estimated at 0.38%. H63D polymorphisms are estimated to have an average allele frequency of 14% and S65C has an estimated frequency of 0.5%. **(Tier 1)**	4	☒ Known ☐ Unknown
Penetrance **OR** **Relative Risk** (include any high risk racial or ethnic subgroups)	A meta-analysis of 19 studies estimates a penetrance of 13.5% (95% CI 13.4-13.6%) for C282Y homozygosity. **(Tier 1)**	4	☐ High (>60%) ☐ Moderate (40-60%) ☒ Low (<40%) ☐ Unknown
	Odds ratios for C282Y homozygosity: • Liver disease: 3.9 (99% CI: 1.9-8.1) • Hepatocellular carcinoma: 11 (99% CI: 3.7-34) • Hepatitis C: 4.1 (99% CI: 1.2-14) • Non-alcoholic liver disease: 10 (99% CI: 2.1-53) **(Tier 1)** *Relative risk cannot be calculated from case control studies. OR represent a good estimate of RR when disease occurrence is infrequent.	10	☒ High (>3) ☐ Moderate (2-3) ☐ Low (<2) ☐ Unknown
Expressivity	Penetrance is higher in male than in female C282Y homozygotes. 26% of females and 32% of males have increased serum ferritin concentrations. 19% of females and 42% of males have been found to have excess liver iron. 38-50% of homozygotes may develop iron overload. 10-33% of homozygotes eventually would develop hemochromatosis-associated morbidity. **(Tier 1)**	4	☒ Known ☐ Unknown
4. How acceptable are the interventions in terms of the burdens or risks placed on the individual?			
Acceptability of Intervention	Phlebotomy is generally thought to have few side effects. Harms were not reported in any studies reviewed by the USPSTF.**(Tier 1)**	1	☐ Very Acceptable ☒ Mildly Acceptable ☐ Risky or problematic
5. Would the underlying risk or condition escape detection prior to harm in the setting of recommended care?			
Chance to escape clinical detection in Adults	It is increasing unusual for individuals with HFE-HH to present with advanced clinical disease (i.e., end-organ damage secondary to iron storage). More typically individuals are determined to have biochemical hemochromatosis (i.e., elevated serum TS and elevated serum ferritin concentration) after evaluation of transferrin-iron saturation and serum ferritin concentration reveals evidence of iron overload. Occasionally, individuals with HFE-HH present whether with early clinical findings of HH such as elevated serum liver enzymes or vague nonspecific symptoms such as abdominal pain, fatigue, arthralgia, and/or decreased libido. **(Tier 4)**	9	☐ Often ☒ Sometimes ☐ Rarely ☐ Unknown

Stage II: Binning Summary

Next Generation Sequencing (NGS) for Adults

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

HH Summary

Recommendation: Routinely report as a clinically actionable incidental finding. This recommendation is limited to individuals homozygous for the C282Y mutation in the *HFE* gene.

Rationale: Hemochromatosis can be a significant health condition, but has very low penetrance. Nevertheless, the estimates of relative risk from case-control studies for various serious complications are high. Interventions for people with increased iron stores are effective. Surveillance for increasing iron stores in asymptomatic C282Y homozygotes is effective in providing for early intervention. The risk for side effects or harms associated with treatment are thought to be small and outweighed by the potential benefits.

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