The Long and Winding Road
Are We Ready for Population Screening for *HFE*-Related Hemochromatosis?

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The long and winding road that leads to your door / Will never disappear, I've seen that road before -- the Beatles

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Historical context

- 1994-1995 – Calls for phenotypic (biochemical) screening for hereditary hemochromatosis (HH)
- 1996 – CDC expert panel favored phenotypic screening of adults for HH
- 1996 – Discovery of C282Y and H63D variants on the \textit{HFE} gene
- 1997 – CDC/NIH meeting, Iron Overload, Public Health and Genetics
- 1998 – Papers from meeting published in journal supplement
  - CDC experts: insufficient evidence on clinical penetrance, accuracy of testing, and ethical, legal, and social issues. Evidence of potential benefit requires data from representative samples of homozygotes (Cogswell, McDonnell, Khoury, et al., \textit{Annals of Internal Medicine} 1998)
My history with HH screening

  - Estimated cumulative risk to age 70 of liver cirrhosis or cancer ~3 times higher than assumed by Rogowski (*Genetics in Medicine* 2009), who concluded screening was not cost-effective
New evidence from UK Biobank analyses – morbidity

- Baseline associations
  - 4-fold risk of liver disease
  - 2-fold risk of osteoporosis or arthritis
  - 50% higher risk of diabetes or pneumonia

- Associations with incident diagnoses similar in magnitude
  - 10-fold risk of liver cancer

- Comments
  - Analysis did not distinguish fibrosis from cirrhosis
  - Demonstration of increased risk of diabetes enabled by large sample
New evidence from UK Biobank analyses – mortality

- UK Biobank analysis
  - Hazard rate of 1.22 (p=0.02) for male homozygotes versus wild type
  - 4% excess risk of death by age 75
  - Finding of excess mortality from first large-scale cohort study
- Studies of prevalence of C282Y homozygotes in older adult samples
  - 4 among 600 (1:150) elderly English men, Willis et al., Lancet 1999
  - Consistent with UK Biobank finding of excess mortality of modest magnitude, despite previous interpretations
Is population screening for HH cost-effective?

- Cost-effectiveness of screening depends on many factors
  - Screening strategy – universal or targeted, one-time or recurrent
  - Prevalence, age of onset, delay of onset of symptoms
  - Cost, uptake, accuracy, and yield of screening
  - Uptake, adherence, and efficacy of prevention strategies
  - How much payers are willing to pay

- More importantly, is screening acceptable to clinicians and patients?
  - Can vary across settings – evidence in US healthcare systems?
Cost-effectiveness analysis of population screening strategies in Australian adults

- De Graaff et al. (*Applied Health Economics and Health Policy* 2017)
- Modeled voluntary screening of adults of northern European ancestry when males turn 30 and females turn 45
- Comparator: Status quo of cascade screening of relatives of patients with HH
- Two broad approaches evaluated to identify C282Y homozygotes
  - Transferrin saturation followed by DNA testing for C282Y variant
  - Molecular testing of C282Y variant in blood or buccal samples
- Results
  - All testing strategies in men appear cost-effective, high detection rates
  - Transferrin saturation testing in women cost-effective, lower detection
Screen for \textit{HFE} homozygotes or iron overload?

- Iron overload can cause serious harm regardless of etiology.
- \textit{HFE}-related hemochromatosis is not the only cause of iron overload, especially among people of non-European ancestry.
- Cases of \textit{HFE}-related hemochromatosis not associated with C282Y homozygosity would be missed by targeted detection of homozygotes.
- Balance of equity and efficiency must be considered in evaluation of population screening strategies.
Implications and questions

- Assumptions would need to be validated in other contexts
- Even if one-time testing for HH appears cost-effective, is it acceptable and feasible?
  - It is acceptable to offer testing based on patient gender and ancestry?
  - What is the uptake of testing and prevention strategies?
  - How will testing results be stored and shared to avoid unnecessary repeat testing while guarding patient confidentiality?
  - Pilot studies in US healthcare systems could provide information
  - Evidence-based guideline would be needed
The findings and conclusions in this presentation have not been formally disseminated by the Centers for Disease Control and Prevention and should not be construed to represent any agency determination or policy.