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 *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., *Annals of Internal Medicine* 1998)

My history with HH screening

- 1998-1999 – Review of 6 cost-effectiveness analyses of screening for HH (Grosse and Teutsch, book chapter, 2000)
- 2008-2009 – Review of cost-effectiveness of screening for HH along with other disorders (Grosse, Rogowski, et al. *Public Health Genomics* 2010)
- 2013-2016 – Modeling of clinical penetrance in terms of severe liver disease (Grosse, Gurrin, et al, *Genetics in Medicine* 2017)
  - 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
  - 2 among 1265 (1:633) Dutch adults ages 85+, van Aken et al. *European Journal of Clinical Investigation* 2002
  - 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 *HFE* homozygotes or iron overload?

- Iron overload can cause serious harm regardless of etiology
- *HFE*-related hemochromatosis is not the only cause of iron overload, especially among people of non-European ancestry
- Cases of *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

For more information, contact CDC
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