Screening for haemochromatosis- evolution of data over 20 years

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Victorian Clinical Genetics Services
## Requirements for an Acceptable Screening Program - Wilson and Jungner, Year - 2000

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<th>Important problem</th>
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Mi-Iron- A randomized patient-blinded study of true versus sham reduction of body iron in HFE related haemochromatosis with moderate iron overload

Do people with HH and SF >300µg/L but less than 1000µg/L need treatment?

- >1 million people in each of US and Europe and >85,000 Australians have or will get SF > 300µg/L but < 1000µg/L due to HFE p.C282Y homozygosity or p.C282Y/p.H63D compound heterozygosity

- Increasing number of commentators advising not to treat HH if SF less than 1000µg/L
To undertake a randomised patient-blinded trial of erythrocytapheresis compared to sham erythrocytapheresis (using plasmapheresis) in individuals who have serum ferritin (SF) $> 300 \mu g/L$ but $<1000 \mu g/L$ (defined here as moderate iron overload) due to HFE p.C282Y homozygosity and to compare the prevalence of symptoms and objective markers of disease in the two treatment arms.
Erythrocytapheresis

- Blood removed
- Spun
- RBCs discarded
- Plasma returned to subject
- Plasmapheresis- opposite
- One treatment removes ~3x RBCs cf venesection
- Reduced hypovolaemia SE cf venesection because of saline replacement
- Anticoagulant can cause SE due to ↓ Ca++ (citrate reaction)
Blinding
Inclusion & exclusion criteria

Inclusion

1. HFE p.C282Y homozygous
2. Aged 18 years or older
3. SF above the upper limit of the normal range (300\(\mu\)g/L) but less than 1000\(\mu\)g/L with a raised TS (>ULN for testing laboratory)

Exclusion

1. HH due to other genotypes
2. Normal SF, SF >1000\(\mu\)g/L or raised SF in the setting of normal TS
3. Other major risk factor(s) for liver toxicity including positivity for hepatitis B or C, excess alcohol consumption (>60g/day in males and 40g/day in females), body mass index >35 (which places the individual at high risk for steatohepatitis)
4. Current or recent venesection for HH (within two years)
5. Pregnant
Outcomes

- **Fatigue**: Modified Fatigue Impact Scale (primary outcome measure)
- **QoL**: SF36 version 2
- **Depression and anxiety symptoms**: Hospital Anxiety and Depression Scale
- **Arthritis**: Arthritis Impact Measurement Scale 2 short form
- **Liver wellbeing**: Hepascore, Fibrometer, Transient elastography - Fibroscan
- **Oxidative stress**: F2 isoprostanes
SF and TS

<table>
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<tr>
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<tr>
<td></td>
<td>Baseline (μg/L)</td>
<td>End of Treatment (μg/L)</td>
<td></td>
</tr>
<tr>
<td>Control (n=44)</td>
<td>509.7 ± 23.7</td>
<td>478.9 ± 25.4</td>
<td></td>
</tr>
<tr>
<td>Treatment (n=50)</td>
<td>518.8 ± 24.6</td>
<td>203.9 ± 10.0</td>
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</table>

Mean difference in change for two groups: p <0.0001

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<th>TS</th>
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<td>Baseline (%)</td>
<td>End of Treatment (%)</td>
<td></td>
</tr>
<tr>
<td>Control (n=44)</td>
<td>63.1 ± 2.7</td>
<td>61.7 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>Treatment (n=50)</td>
<td>63.7 ± 2.3</td>
<td>45.4 ± 2.3</td>
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Mean difference in change for two groups : p <0.01
## Modified Fatigue Impact Scale

<table>
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<tr>
<th></th>
<th>N</th>
<th>ΔControl</th>
<th>ΔTreatment</th>
<th>Adjusted Mean Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MFIS Total</strong></td>
<td>93</td>
<td>-1.35 (1.74)</td>
<td>-6.82 (1.61)</td>
<td>-6.25 (2.46)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>MFIS: Cognitive</strong></td>
<td>94</td>
<td>-0.80 (0.83)</td>
<td>-3.90 (0.78)</td>
<td>-3.60 (1.16)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>MFIS: Physical</strong></td>
<td>93</td>
<td>-0.60 (0.89)</td>
<td>-2.34 (0.83)</td>
<td>-1.93 (1.29)</td>
<td>0.14</td>
</tr>
<tr>
<td><strong>MFIS: Psychosocial</strong></td>
<td>94</td>
<td>-0.07 (0.23)</td>
<td>-0.58 (0.22)</td>
<td>-0.54 (0.33)</td>
<td>0.10</td>
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Other outcomes

- No significant change in SF36v2, HADS
- Significant improvement in AIMS2-SF affect (p<0.03)
- Significant improvements in hepascore (p<0.05) and plasma F₂ isoprostanes (p<0.05)
How successful was blinding?

“Do you think your iron level was reduced?”

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<tr>
<td>Yes</td>
<td>10 (22.7%)</td>
<td>10 (20%)</td>
<td></td>
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<tr>
<td>No</td>
<td>6 (13.6%)</td>
<td>9 (18%)</td>
<td>0.603</td>
</tr>
<tr>
<td>Not sure</td>
<td>28 (63.6%)</td>
<td>29 (58%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>0 (0%)</td>
<td>2 (4%)</td>
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Improvement in control v treatment groups

- 13/14 patient reported outcome comparisons improved in treatment group more than controls (p=0.01)

- All significant changes were where treatment group improved more than controls

- No changes that were greater in the controls were significant
Conclusions

- Well blinded study
- Significant improvement in the treatment group in the MFIS total score and cognitive component and affect component of the arthritis scale
- No change in overall SF36v2 (MCS & PCS) or HADS
- Significant improvement in hepascore and isoprostanes
Conclusions...

- Treatment of raised SF is generally safe
- Data from this study indicates clinical benefit
- All with raised SF should have normalisation of body iron as indicated by normal SF
Haemscreen

- **Aims**

  - screen 10,000 individuals in their workplace for HFE p.C282Y
  - assess whether a “worried well” population results
  - assess consent in the setting of one to many education
  - minimise illness due to hemochromatosis
Results

- 11,923 attended (11,841 eligible), 11,306 screened (53.1% female) = 95.5% uptake

- 51 p.C282Y homozygotes

- No change in SF36, STAI from pre screening to post result in p.C282Y homozygotes

- All with raised iron took steps to normalise iron indices
Is screening for HH in late high school students acceptable and feasible?

HaemScreen- about 10% of eligible individuals had screening

School is an ideal place to:
  - teach students about genetic health
  - reach a high percentage of the population with relative ease
  - empower young people to control future health
Results...

- 17,638 offered, 5757 had screening (uptake 32.6%)
- 28 p.C282Y homozygotes identified
- No change in SF36, STAI from pre screening to post result in p.C282Y homozygotes
Health economics

- De Graaff et al Appl Health Econ Health Policy 2017

- Modelled screening by genotype and by TS

- Both cost effective for males, TS screening cost effective for females

- BUT costs for genotyping excessive
## Requirements for an Acceptable Screening Program - Wilson and Jungner, Year- 2020

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The case for screening for hemochromatosis is increasingly strong. There is much more data on:
- Natural history, especially from UKB
- Treatment response: RCT in moderate iron overload
- Response to screening

When and how?
- Opportunistic through primary health care, people having genomic testing for another reason
- Stand alone- high school, home testing (akin to bowel cancer screening)
- At time of reproductive carrier screening
- Secondary prevention – clinical screening re arthritis/osteoporosis, chronic pain, diabetes, etc