the cascade screening in The Netherlands experience

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disclosures:

consultant to Vascular Research Network
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Outline

- Why FH
- How to screen
- Results
- Knowledge gaps
- Cost effectiveness
Why Familial Hypercholesterolemia?

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- **Common genetic abnormality:**
  
  1 in 250 to 500 (0.2-0.4%) in most populations

- **Associated with significant mortality and morbidity:**
  
  in men, clinical CAD in:  
  
  - 5% by age 30 yrs
  - 20% by age 40 yrs
  - 60% by age 50 yrs
  - 85% by age 60 yrs

Why Familial Hypercholesterolemia?

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FH in the USA:

- At 1 in 500 = 618,150 Americans with FH
- At 1 in 250 = 1,236,300 Americans with FH
- More Frequent than Cystic Fibrosis, Type I Diabetes and Neonatal Hypothyroidism
- As LETHAL as AIDS if NOT TREATED

Why Familial Hypercholesterolemia?

Effect on families with FH

Lovastatin trial in children

132 Adolescent males (10-16 yrs) with FH:
97 with family history:

• FH in 56% mothers; 44% fathers
• CAD present in 37%:
  - 59% of fathers
  - 19% of mothers
• Mean onset CAD 37 yrs
• 20% of fathers with FH dead due to CAD

Stein EA, et al. JAMA 1999; 281: 137-144
Why Familial Hypercholesterolemia?

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Why Familial Hypercholesterolemia?

FH is the most frequent genetic metabolic disorder

Most FH is undiagnosed and untreated

Easily Diagnosed:
- Family History
- Lipid Profile
- Genetic testing

Treatable:
- Marked reduction mortality and morbidity by lowering cholesterol
**Dutch Lipid Clinic Network Criteria**

**Family history**
- a. first degree relative with premature CVD* 1
- b. first degree relative with LDL>95th perc. 1
  - and / or
- a. first degree relative with Tx and/or arcus 2
- b. children below 18 with LDL>95th perc. 2

**Clinical history**
- a. patient has premature CAD* 2
- b. patient has premature cerebr. or PAD* 1

**Physical examination**
- a. tendon xanthomata 6
- b. arcus cornealis (<45 yrs.) 4

**Laboratory analysis**
- a. LDL-cholesterol >328 mg/dl (>8.5) 8
- b. LDL-cholesterol: 250-328 mg/dl (6.5-8.4) 5
- c. LDL-cholesterol: 193-250 mg/dl (5.0-6.4) 3
- d. LDL-cholesterol: 155-193 mg/dl (4.0-4.9) 1

**DNA-analysis**
- a. functional mutation in LDL-receptor gene 8

**Diagnosis of FH is:**
- certain when ≥8 points
- probable when 6-7 points
- possible when 3-5 points

*: men<55 yrs, women<60 yrs
LDL cholesterol:

- <30 yrs: 5.96 mmol/l
- 30-39 yrs: 6.17 mmol/l
- 40-49 yrs: 6.74 mmol/l
- >49 yrs: 6.61 mmol/l

LDL cholesterol:

- <30 yrs: 230 mg/dl
- 30-39 yrs: 238 mg/dl
- 40-49 yrs: 260 mg/dl
- >49 yrs: 255 mg/dl

Civeira et al. Am J Cardiol 2008;102:1187-1193
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Fig 4 | Kaplan-Meier curve estimates of cumulative myocardial infarct-free survival among patients with familial hypercholesterolaemia older than 55 years according to statin treatment compared with a sample from the general population (Rotterdam study). (P<0.001 for difference between untreated patients and general population; P=0.07 for difference between treated patients and general population)

Versmissen et al. BMJ. 2008; 337: a242
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Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease

Consensus Statement of the European Atherosclerosis Society

Conclusion

Owing to severe underdiagnosis and undertreatment of FH, there is an urgent worldwide need for diagnostic screening together with early and aggressive treatment of this extremely high-risk condition.

• genetic cascade screening over universal screening

• centrally co-ordinated

• aim for first, second and third degree relatives

• lack of DNA testing should not preclude phenotypical screening
Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation


4.1 Notification of relatives at risk of FH should generally not be carried out without the consent of the index case. [3A]
4.2 Relatives should only be directly notified of their risk without consent of the index case if there is specific legislative provision for breach of confidentiality in the relevant jurisdiction. [3C]
4.3 A proactive approach that respects the principles of privacy, justice and autonomy is required. [3A]
4.4 Pre-testing counselling should be offered to at risk family members of an index case prior to any form of testing. [1A]
4.5 Systematic cascade screening should ideally be co-ordinated by a dedicated centre and should not be carried out in primary care without central co-ordination, particularly if employing DNA testing. [1B]
4.6 Cascade screening of families should be carried out using both a phenotypic and genotypic strategy, but if DNA testing is not available a phenotypic strategy alone should be used [1A]
4.7 Cascade screening should initially be carried out as a priority in first-degree relatives and then extended to second- and third-degree relatives. [1A]
4.8 In the absence of genetic testing, the diagnosis of FH should be made in close relatives using age-, gender- and country-specific plasma LDL-cholesterol levels. Diagnostic clinical tools for index cases, such as the Dutch Lipid Clinic Network and Simon Broome criteria, should not be employed to make the diagnosis of FH in relatives [1A]
4.9 DNA testing makes cascade screening more cost-effective and should be employed to screen family members after the mutation is identified in the index case. [1A]
4.10 Children with xanthomata or other physical findings of homozygous FH, or at risk of homozygous FH should be screened as early as possible and definitely by 2 years of age. [2A]
4.11 Children with suspected heterozygous FH should be screened between the ages of 5 and 10 years; age at screening should be similar in boys and girls. [2B]
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case-finding approaches

1. contact relatives by phone or letter via index case (USA)
2. index case contacts relatives to visit GP (Germany)
3. have relatives come to Lipid Clinic (most countries)
4. genealogical investigation and DNA testing (Iceland)
5. active family investigation by GFW and genetic testing (Netherlands, Spain, UK)
6. any combination of the above
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Active, nation-wide, programs ongoing in:

Netherlands  Spain  UK (Wales, Scotland, N-Ireland)  Uruguay

Advanced, regional, programs in:

Australia  Brazil  Czech Republic  Iceland  New Zealand  Norway  Slovak Republic  Slovenia

Successful, local, initiatives in:

Austria  Germany  Ireland  Italy  Malaysia  Poland  Portugal  Switzerland  Taiwan
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case-finding and genetic field work - MED PED:

Make Early Diagnosis to Prevent Early Death

1. identify index patients by DNA diagnosis (I.C.)
2. contact index patient and 1st degree relatives (house visit)
3. collect blood samples
4. analyse for familial mutation and test cholesterol
5. identify new patients
6. contact more relatives (2nd and 3rd degree)
Identification of index cases

Clinical + DNA-diagnosis
Genetic Field Work
Genetic Field Work – house visit and blood sampling
Genetic Field Work - collect family data
FAMILIAL HYPERCHOLESTEROLEMIA

Pedigree of a large FH-Afrikaner kindred
Genetic Field Work – house visit and blood sampling
DNA test

**PCR formulier nr.______**

**mutatie:** E207K/X/Q

<table>
<thead>
<tr>
<th>laan</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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<td>35892</td>
<td>35738</td>
<td>32983</td>
<td>18997</td>
<td>22998</td>
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<td>+/−</td>
<td>−/−</td>
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<tr>
<td>result.</td>
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**uitslag / opmerkingen**

35668 in E207K
30738 in E207X
32983 in E207X
22998 in E207Q = neg

(foto van de gel)

G:\DIVG\EVG\Formulieren\MEVG\Formulieren\pcr form, versie 1.1, 04-08-2004
Referral to Lipid Clinic
annual report 2012
estimated incidence: 1:400
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results

actual numbers (April 30, 2014)

| genetic cascade screening: 60165 individuals tested | 21549 cases (36%) |
| Lipid Clinics: molecular genetic testing | 5958 index cases |
| clinical diagnosis only | 19145 cases |
| estimated number of cases detected:¹ | 46652 cases |
| at 1:500 | 33686 | 138% |
| at 1:400 | 42108 | 111% |
| at 1:319² | 52800 | 88% |
| at 1:232³ | 72600 | 64% |
| at 1:200⁴ | 84216 | 55% |

¹: 16,843 181 population, March 2014; Central Bureau for Statistics; www.cbs.nl
²: Sjouke et al. Eur Heart J 2014
⁴: Nordestgaard et al. Eur Heart J 2013;34:3478-3490
Ingredients for successful cascade testing in The Netherlands

- **action**: active approach in contacting family members of index cases
- **convenient**: screenees have to do nothing; they are visited at home or at their place of work
- **costs**: the test is free of charge
- **certain**: the test result is unequivocal
- **comfort/reassurance**: 64% of the individuals tested is not a carrier and will not pass the disorder on to their children
- **control**: 36% of the individuals is a carrier and is better motivated to start medication and life style modifications to manage their now clearly identified cardiovascular risk
- **central**: central co-ordinating screening organisation and central DNA-testing laboratory
- **coverage**: national network of Lipid Clinics and nation-wide coverage
Review of the first 5 years of screening for familial hypercholesterolaemia in the Netherlands.  

Mortality over two centuries in a large pedigree with familial hypercholesterolaemia: family tree mortality study.  

Parental attitude towards genetic testing for familial hypercholesterolemia in children.  

Low-Density Lipoprotein-receptor gene mutations and cardiovascular risk in a large genetic cascade screening population.  
*Circulation* 2002; 106: 3031-3036.

Long term compliance to lipid lowering medication after genetic screening for Familial hypercholesterolemia.  

Cost-effectiveness analysis of the genetic screening program for Familial hypercholesterolemia in the Netherlands.  

Genetic determinants of cardiovascular disease risk in Familial Hypercholesterolemia.  

Influence of LDL-receptor mutation type on age of onset of cardiovascular events in patients with familial hypercholesterolaemia.  

Functionality of sequence variants in the genes coding for the low-density lipoprotein receptor and apolipoprotein B in individuals with inherited hypercholesterolemia.  
*Hum Mutat.* 2010;31:752-760.

Molecular Basis of Autosomal Dominant Hypercholesterolemia: Assessment in a Large Cohort of Hypercholesterolemic Children.  

Founder mutations in the Netherlands: geographical distribution of the most prevalent mutations in the low-density lipoprotein receptor and apolipoprotein B genes.  
*Neth Heart J.* 2011:175-182.

Maternal inheritance of familial hypercholesterolemia caused by the V408M low-density lipoprotein receptor mutation increases mortality.  

Genetic variation in APOB, PCSK9, and ANGPTL3 in carriers of pathogenic autosomal dominant hypercholesterolemic mutations with unexpected low LDL-CI Levels.  

Cardiovascular risk in relation to functionality of sequence variants in the gene coding for the low-density lipoprotein receptor: a study among 29,365 individuals tested for 64 specific low-density lipoprotein-receptor sequence variants.  
*Eur Heart J.* 2012;33(18):2325-2330.

Quality assessment of the genetic test for familial hypercholesterolemia in the Netherlands.  
*Cholesterol.* 2013;2013:531658.
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knowledge gaps

• CVD risk index cases vs. free living population
• value of age at identification
• genetic diagnosis vs clinical diagnosis
• CVD risk in mutation carriers with normal LDL
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knowledge gap: CVD risk index cases vs. free living population

cholesterol levels in FH index cases and in a Free Living population

1: Am J Cardiol 2002; 90: 181
2: Am J Cardiol 2003; 91: 604
3: J Int Med 2004; 256: 486
4: Lancet 2001:357:165-168
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knowledge gap: value of age at identification

Maternal inheritance of familial hypercholesterolemia caused by the V408M low-density lipoprotein receptor mutation increases mortality


1 Department of Internal Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands
2 Department of Vascular Medicine, Academic Medical Center, Amsterdam, The Netherlands

Table 1

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Person years</th>
<th>Observed deaths</th>
<th>Expected deaths</th>
<th>SMR</th>
<th>95% CI</th>
<th>P value</th>
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<td>Maternal inheritance</td>
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<td></td>
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<tr>
<td>Overall</td>
<td>58</td>
<td>1539</td>
<td>17</td>
<td>6.83</td>
<td>2.49</td>
<td>1.45–3.99</td>
<td>0.001</td>
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<td>Males</td>
<td>27</td>
<td>733</td>
<td>9</td>
<td>3.35</td>
<td>2.69</td>
<td>1.23–5.10</td>
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<tr>
<td>Females</td>
<td>31</td>
<td>805</td>
<td>8</td>
<td>3.48</td>
<td>2.30</td>
<td>0.99–4.53</td>
<td>0.026</td>
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<tr>
<td>Paternal inheritance</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Overall</td>
<td>55</td>
<td>1484</td>
<td>11</td>
<td>8.5</td>
<td>1.30</td>
<td>0.65–2.32</td>
<td>0.23</td>
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<tr>
<td>Males</td>
<td>26</td>
<td>714</td>
<td>7</td>
<td>3.8</td>
<td>1.84</td>
<td>0.74–3.79</td>
<td>0.092</td>
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<tr>
<td>Females</td>
<td>29</td>
<td>770</td>
<td>4</td>
<td>4.7</td>
<td>0.86</td>
<td>0.23–2.18</td>
<td>0.68</td>
</tr>
</tbody>
</table>

n, number of persons at risk; SMR, standardized mortality ratio; 95% CI, 95% confidence interval.

Patients who inherited FH maternally had 2.2 times higher mortality risk relative to those who inherited it paternally (95% CI 1.01–4.08; p = 0.048).

Results: Maternally inherited FH was associated with significantly higher excess mortality than FH transmitted by fathers (relative risk 2.2; p = 0.048): the SMR of maternal inheritance was 2.49 (95% confidence interval CI 1.45–3.99; p = 0.001), whereas it was not significantly increased in paternally inherited FH (SMR 1.30, 95% CI 0.65–2.32; p = 0.234).

Conclusion: Mortality rates are more increased when FH is inherited through the mother, supporting the fetal origin of adulthood disease hypothesis with all cause death, the most indisputable outcome measure. Future research should explore safe options for cholesterol-lowering therapy of pregnant women with FH in order to prevent unfavourable (epigenetic) consequences leading to atherosclerosis in their children.
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knowledge gap: value of age at identification

Circulation 2004; 109(S):III33-8
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knowledge gap: genetic diagnosis vs clinical diagnosis

- time of exposure
- type of mutation
- patient’s perception
- physician’s perception
- family screening
- offspring
1.0
1.5
2.0
2.5
3.0
3.5
0.00
-0.04
-0.08
-0.12
-0.16
-0.20

mean difference in LDL cholesterol (mmol/L)
mean difference in HDL cholesterol (mmol/L)

cases
relatives
185 393
51 173
38 163
39 148
54 223
345 825
243 450

combo: N543H + 2393del9

Atherosclerosis 2005;180:93-99
knowledge gap: genetic diagnosis vs clinical diagnosis

mutations and CVD risk

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>RR*</th>
<th>95% CI</th>
<th>p</th>
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<tr>
<td>FH</td>
<td>608/1101</td>
<td>8.45</td>
<td>5.15-13.84</td>
<td>&lt;0.0001</td>
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<td>N543H/2393del9</td>
<td>241/401</td>
<td>7.72</td>
<td>3.06-19.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>V408M</td>
<td>77/181</td>
<td>8.08</td>
<td>2.34-27.96</td>
<td>&lt;0.0001</td>
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<td>1359-1</td>
<td>102/176</td>
<td>15.04</td>
<td>5.12-44.23</td>
<td>&lt;0.0001</td>
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<tr>
<td>313+1/2</td>
<td>83/151</td>
<td>10.95</td>
<td>4.56-26.25</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Atherosclerosis 2005;180:93-99
knowledge gap: genetic diagnosis vs clinical diagnosis

- unaffected relatives
- FH: N543H/2393del9 mutation
- FH: all other mutations

Atherosclerosis 2005;180:93-99
knowledge gap: CVD risk in mutation carriers with normal LDL

- 45 jr
  - TC 7.6
  - LDL 5.8
  - HDL 0.62
  - TG 1.64
  - >P95
  - >P95
  - P40
  - P65

- 50 jr
  - TC 3.3
  - LDL 1.0
  - HDL 2.12
  - TG 0.47
  - <P5
  - P5
  - P85
  - <P5

- 17 jr
  - TC 5.1
  - LDL 2.4
  - HDL 1.19
  - TG 1.47

- 14 jr
  - TC 3.1
  - LDL 0.4
  - HDL 2.67
  - TG 0.05

- 14 jr
  - TC 3.7
  - LDL 2.4
  - HDL 1.24
  - TG 0.22

- 12 jr
  - TC 5.83
  - LDL 4.35
  - HDL 1.24
  - TG 0.35

- normal LDL
- high LDL → R3500Q in APOB
- low LDL → 11712delC in APOB

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IS MOLECULAR GENETIC TESTING COST EFFECTIVE?

cost effectiveness of molecular genetic testing:

costs:
• testing (index + relatives; lab + GFW)
• medical examination and follow-up
• lifetime medication
• treatment CVD events

taking into account:
• RR disease/death, treated/untreated
• gender and age
• medication type, dosage, price, frequency
• occurrence of CVD and treatment
• discounting at 4%
Costs of genetic testing in 2006:

- 2000 complex DNA Dx (€ 645; $929): € 1,290,000; $1,858,000
- 6154 single mutation tests (€ 95; $137): € 584,630; $843,098
- Operating costs foundation: € 1,412,565; $2,034,094

Total: € 3,287,195; $4,735,192

2317 cases: € 1419 or $2043 per case
### Table: Cost and Frequency of Statin Doses

<table>
<thead>
<tr>
<th>Statin</th>
<th>Dose (mg/day)</th>
<th>Frequency in Sample</th>
<th>Relative Freq.</th>
<th>Cost ($/month)</th>
<th>Freq. x Cost ($)</th>
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<td>Atorvastatin</td>
<td>10</td>
<td>35</td>
<td>7.0%</td>
<td>32.08</td>
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<td></td>
<td>20</td>
<td>126</td>
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<td>49.36</td>
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<td>1</td>
<td>0.2%</td>
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<td>61</td>
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<td>78.49</td>
<td>9.58</td>
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<td></td>
<td>60</td>
<td>5</td>
<td>1.0%</td>
<td>127.84</td>
<td>1.28</td>
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<td>Simvastatin</td>
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<td>89</td>
<td>17.8%</td>
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<td>106</td>
<td>21.2%</td>
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<td>12</td>
<td>2.4%</td>
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<td>30</td>
<td>6.0%</td>
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<td>Pravastatin</td>
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<td>3.4%</td>
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<td>1.09</td>
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<td>2</td>
<td>0.4%</td>
<td>54.73</td>
<td>0.22</td>
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**Total**

|               | 500 | 100 | 46.07 |

Cost per year: $46.07 \times 12 = $553

£242

€383
### The cascade screening in The Netherlands experience

<table>
<thead>
<tr>
<th>age-sex group (at time of Dx)</th>
<th>weighting for age-sex group (%)</th>
<th>screening cost ($)</th>
<th>lifetime drug cost* ($)</th>
<th>-statin treatment</th>
<th>+statin treatment</th>
<th>increment</th>
<th>total incremental cost** ($)</th>
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<td>male</td>
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<td>5418</td>
<td>1795</td>
<td>1185</td>
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Incremental cost per new untreated case diagnosed. *: discounted at 4%  
**: screening cost + lifetime drug cost + increment cost of treating events.

Semin Vasc Med 2004;4:97-104
### life-years gained by treatment

<table>
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<th>men (yrs)</th>
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<th>discounted at 4%</th>
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<table>
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<th>women (yrs)</th>
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</tbody>
</table>

| All         | 3.3      | 0.9              |

### cost per life-year gained

- **$2000**
- **$8310**
- **£876**
- **£3640**
- **€1387**
- **€5762**

*the cascade screening in The Netherlands experience*

*Semin Vasc Med 2004;4:97-104*
the cascade screening in The Netherlands experience

Cost per life year gained (USA)

www.khamaid.org:

- HIV blood tests for sex workers: $3.35
- Training for midwives in Kham: $8.40
- Anti retro-viral drugs for HIV+ people: $1317
- Smoking cessation intervention: $2,587
- Chlorination of water supplies: $4,000
- PAP smear every three years: $4,079
- Colonoscopy every ten years: $7,000
- FH DNA testing and treatment: $8,310
- Hepatitis vaccination: $20,000
- Breast cancer screening: $40,000
- Airbags in cars: $40,000
- Neonatal intensive care: $50,000
- Home radon testing: $140,000
- Heart transplant: $157,000.
- Seat belts in the rear seats of cars: $1,944,000
- Seat belts in school buses: $2,760,000

*NEJM 1997;366:322-336
*Semin Vasc Med 2004;4:97-104
National FH screening: the Dutch experience

conclusions

• Screening cost: $1768; £774; €1226
• Life long drug cost: $6790; £2974; €4708
• Incremental cost: $7479; £3276; €5186 (disc. 4%)
• Cost per life-year gained: $8310; £3640; €5762 (disc. 4%)

MOLECULAR GENETIC TESTING IS COST EFFECTIVE!
National FH screening: the Dutch experience

summary

1. effective: 1 index → 20 relatives → 8 new patients
2. DNA-analysis AND cholesterol testing
3. 93% on meds after 1 year, 80% after 2 years
4. treatment timely (mean age 37.5 yrs)
5. Lipid Clinic FH more severe than FLP FH (score list does not apply)
6. positive attitude (98% participation, 85% positive)
7. cholesterol reduction should be better
8. relation mutation - cholesterol and CVD risk
9. education public and physicians
10. cost-effective
Inferior doctors treat the full blown disease
Mediocre doctors treat the disease before evident
Superior doctors prevent the disease

-Huang Dee: Nai-Ching (2600 B.C., first Chinese medical text)