POPULATION SCREENING

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University Medical Center Groningen
The Netherlands
DISCLOSURES

• Grant support
  - Dutch Kidney Foundation
  - Dutch Ministry of Economic Affairs
  - KPN *(telecommunication services)*
  - E-Zorg *(provider internet based secured health care platform)*
  - Copernicus *(e-health IT specialist)*
  - Hessels-Grob *(manufacturer PeeSpot urine collection device)*
  - Healthy.io *(manufacturer ACR app)*
Strategies for screening
Which population to screen?

1. Opportunistic, clinic based screening of high risk individuals
   - Diabetes mellitus
   - Hypertension
   - Cardiovascular disease history
   - (Concomitant disease predisposing for CKD: SLE, RA …)
   - (Elderly, i.e. age > ? years)
   - (Family history of CKD)
   - (Low SES, how to operationalize?)
   - (Specific ethnic subgroups)

   Screening may not lead to major treatment changes in most patients

2. Lab registry data (to determine CKD prevalence / progressive CKD)?

3. Entire population?
Strategies for screening
Is screen + treatment effective for ESKD prevention?

Screen and treatment program begins

Number of events

- Number of new ESKD cases
- Number of deaths

Terminal events per 100 person-years

ACR categories, g/mol

Control
Treatment

<34  34 - 99  99 - 199  200+

Terminal events per 100 person-years

Screen and treat for CKD program
Australian aboriginals Tiwi Islands

Hoy, Wang et al
Kidney Int 2003
Strategies for screening
Screening lab registries for progressive CKD

HEFT experience (leading to the ASSIST-CKD protocol)
Flagging progressive CKD based on eGFR data in registries + giving advice

Rayner, Gallagher et al
NDT 2014, BMC Nephrol 2017
Strategies for screening
Screening lab registries for (progressive) CKD


Integrating Risk-Based Care for Patients With Chronic Kidney Disease in the Community: Study Protocol for a Cluster Randomized Trial. Harasemiw … Tangri. Can J Kidney Health Dis. 2019

Effect of 2 Clinical Decision Support Strategies on Chronic Kidney Disease Outcomes in Primary Care: A Cluster Randomized Trial. Carroll … Fox. JAMA Netw Open. 2018


Improving Care for Patients With or at Risk for Chronic Kidney Disease Using Electronic Medical Record Interventions: A Pragmatic Cluster-Randomized Trial Protocol. Nash … Tu. Can J Kidney Health Dis. 2017


Etc, etc
Using registry data for screening
What to screen for?

Average of NHANES (n=18,026) and PREVEND (n=8,592)

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Albuminuria</th>
<th>Unknown</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2</td>
<td></td>
<td>Unknown</td>
<td>89.6</td>
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<td>0.5</td>
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<tr>
<td>3a</td>
<td></td>
<td>Unknown</td>
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<td>0.6</td>
<td>0.2</td>
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<tr>
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<td></td>
<td>Unknown</td>
<td>0.8</td>
<td>0.4</td>
<td>0.2</td>
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<tr>
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<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
</tr>
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</table>

Dutch General Practioner practices (n=214,817)

<table>
<thead>
<tr>
<th>eGFR</th>
<th>Albuminuria</th>
<th>Unknown</th>
<th>1/2</th>
<th>3a</th>
<th>3b</th>
<th>4</th>
<th>5</th>
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<tbody>
<tr>
<td>1/2</td>
<td></td>
<td>Unknown</td>
<td>1.1</td>
<td>1.9</td>
<td>0.4</td>
<td>0.1</td>
<td>0.0</td>
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<tr>
<td>3a</td>
<td></td>
<td>Unknown</td>
<td>0.2</td>
<td>0.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>3b</td>
<td></td>
<td>Unknown</td>
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<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td>0.0</td>
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<tr>
<td>4</td>
<td></td>
<td>Unknown</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
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<td>0</td>
<td>0</td>
<td>0</td>
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</table>

Population average

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unknown</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>10.4%</td>
<td>minus</td>
<td>5.8%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>5.6%</td>
<td>minus</td>
<td>4.5%</td>
<td>minus</td>
</tr>
<tr>
<td>ACR &gt;30</td>
<td>6.6%</td>
<td>minus</td>
<td>2.1%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &gt;60 + ACR&gt;30</td>
<td>4.8%</td>
<td>minus</td>
<td>1.3%</td>
<td>minus</td>
</tr>
</tbody>
</table>

Known by GPs

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unknown</th>
<th>1</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>CKD</td>
<td>5.8%</td>
<td>minus</td>
<td>4.6%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>4.5%</td>
<td>minus</td>
<td>1.1%</td>
<td>minus</td>
</tr>
<tr>
<td>ACR &gt;30</td>
<td>2.1%</td>
<td>minus</td>
<td>4.4%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &gt;60 + ACR&gt;30</td>
<td>1.3%</td>
<td>minus</td>
<td>3.5%</td>
<td>minus</td>
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</tbody>
</table>

Yet missing, to be found by screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>Unknown</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>4.6%</td>
<td>minus</td>
<td>1.1%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &lt;60</td>
<td>1.1%</td>
<td>minus</td>
<td>4.4%</td>
<td>minus</td>
</tr>
<tr>
<td>ACR &gt;30</td>
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<td>minus</td>
<td>3.5%</td>
<td>minus</td>
</tr>
<tr>
<td>eGFR &gt;60 + ACR&gt;30</td>
<td>3.5%</td>
<td>minus</td>
<td>3.5%</td>
<td>minus</td>
</tr>
</tbody>
</table>
What do we screen for?
Low eGFR or high ACR?

Kidney function

Need for kidney function replacement therapy

Follow-up (in years)
What do we screen for?
Low eGFR or high ACR?

Baseline proteinuria (g/d) vs Relative risk for ESKD

ACEi better vs Control better

Meta-analysis, 11 studies ACEi vs control
N = 1860, primary renal disease

Jafar et al
Ann Int Med 2001
Effect of lipid lowering dependent on baseline eGFR

<table>
<thead>
<tr>
<th>Number of events (% per annum)</th>
<th>RR (CI) per 1-0 mmol/L reduction in LDL cholesterol</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin or more intensive regimen</td>
<td>Control or less intensive regimen</td>
<td></td>
</tr>
<tr>
<td><strong>Major coronary event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min per 1.73 m²</td>
<td>3200 (1.2%)</td>
<td>4178 (1.6%)</td>
</tr>
<tr>
<td>eGFR 45 to &lt;60 mL/min per 1.73 m²</td>
<td>1157 (1.7%)</td>
<td>1479 (2.2%)</td>
</tr>
<tr>
<td>eGFR 30 to &lt;45 mL/min per 1.73 m²</td>
<td>457 (2.3%)</td>
<td>567 (2.8%)</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min per 1.73 m² not on dialysis</td>
<td>163 (1.5%)</td>
<td>179 (1.7%)</td>
</tr>
<tr>
<td>On dialysis</td>
<td>264 (2.1%)</td>
<td>287 (2.3%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>5303 (1.4%)</td>
<td>6761 (1.8%)</td>
</tr>
<tr>
<td><strong>Major vascular event</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eGFR ≥60 mL/min per 1.73 m²</td>
<td>7348 (2.9%)</td>
<td>8933 (3.6%)</td>
</tr>
<tr>
<td>eGFR 45 to &lt;60 mL/min per 1.73 m²</td>
<td>2377 (3.6%)</td>
<td>3013 (4.6%)</td>
</tr>
<tr>
<td>eGFR 30 to &lt;45 mL/min per 1.73 m²</td>
<td>863 (4.5%)</td>
<td>1014 (5.2%)</td>
</tr>
<tr>
<td>eGFR &lt;30 mL/min per 1.73 m² not on dialysis</td>
<td>320 (3.0%)</td>
<td>364 (3.5%)</td>
</tr>
<tr>
<td>On dialysis</td>
<td>571 (4.7%)</td>
<td>599 (5.0%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>11617 (3.2%)</td>
<td>14079 (3.9%)</td>
</tr>
</tbody>
</table>

Meta-analysis of individual participant data
N=28 trials studying statins, including 183,419 participants

Cholesterol Treatment Trialists Collaboration
Lancet Diabetes Endocrinol 2016
Why CKD causes CVD
The worse eGFR, the more causal mechanisms

- Obesity
- Smoking
- Diabetes
- High blood pressure
- High calcium
- High phosphate
- Sodium retention
- Chronic inflammation
- Anemia
- Uremic toxins
- Metabolic acidosis
- Hyperparathyroidism
- Sympathetic overactivity
- etc etc etc
- Dialyzer leucocyte activation
- Hemodynamic stress by shunt
- etc etc etc

Gansevoort et al, Lancet 2013
Death due to CKD and colorectal cancer

Percentage of overall mortality in the EU

- End-Stage Kidney Disease: 1.8%
- Colorectal cancer: 3.4%
- Cardiovascular disease caused by CKD: 2.7%

WHO Global Burden of Disease consortium
https://vizhub.healthdata.org/gbd-compare/
Population screening for colorectal cancer

TO: Central laboratory for population screening

Colorectal cancer?
The WHO Wilson and Jungner criteria for population screening

1. **✓** The condition to screen for is an important health problem
2. **✓** There is a recognizable or early symptomatic stage of the condition
3. **✓** There is a reliable screenings method
4. **✓** The screenings method is acceptable for the population
5. **✓** The natural course of the disease is known
6. **✓** The process of screening is a continuous process
7. **✓** There is consensus on the question who should be treated
8. **✓** There is a generally accepted treatment for the condition
9. **?** There are sufficient services and finances for diagnosis and treatment
10. **✓** The costs of screening, diagnostics and treatment relate favorably to the costs of health care in total

Wilson en Junger, WHO 1968
Alderman et al, WHO 2008
Cost-Effectiveness of CKD screening  
Systematic reviews

_Crews et al, Adv Chronic Kidney Dis 2011_

“The ACR test is cost-effective to screen individuals at high risk for CKD and should be considered for those at high risk for CVD.”

“Data are emerging that population screening for albuminuria may be especially cost-effective in identifying high risk-aptients who are not yet treated and therefore most likely to benefit of screening and subsequent treatment.”
Cost-Effectiveness of CKD screening
Additional specific considerations

Screening only HT, DM or CVD+ may not lead to a major change in Tx

**Efficacy**

- Most CE studies took only prevention of ESKD into account
- Benefit with respect to CVD prevention should also be incorporated

**Costs**

- Most CE studies modelled screening by GPs (= high costs)
- Cheaper screening strategies are possible
  - Home based screening (self tests)
  - Combination screening
Population screening for colorectal cancer + CKD combined?

Chronic Kidney Disease?  Colorectal cancer?

TO: Central laboratory for population screening
Population screening for albuminuria
To detect novel CVD/CKD risk factors

PREVEND study: 85,473 subjects invited for urine screening, of which 40,856 responded. Of these 7.5% had elevated UAC, and 4.0% on confirmation by two 24hr urines.

Ozyilmaz et al, NDT 2010
Population screening for albuminuria
Prevalence in those without elevated albuminuria

PREVEND study: 85,473 subjects invited for urine screening, of which 40,856 responded
Of these 7.5% had elevated UAC, and 4.0% on confirmation by two 24hr urines

Ozyilmaz et al
NDT 2010
Population screening for albuminuria
To detect risk for CV events

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>No</th>
<th>New</th>
<th>Known</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>5442</td>
<td>1263</td>
<td>616</td>
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<tr>
<td>Events</td>
<td>139</td>
<td>112</td>
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</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
<th>No</th>
<th>New</th>
<th>Known</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>320</td>
<td>328</td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>26</td>
<td>50</td>
<td>40</td>
</tr>
</tbody>
</table>

PREVEND study, N=8,592 participants
Observational, general population based screening for albuminuria

Ozyilmaz et al
NDT 2013
Population screening for albuminuria
To detect risk for CKD progression

PREVEND study, N=8,592 participants
Observational, general population based screening for albuminuria

Ozyilmaz et al
NDT 2017
Implementation research
N=15,000 participants
Urine test

City of Breda

"Classical" method

"Novel" method
THOMAS
Screening method A: “classical”

Identification label (bar code coupled to participant)

Logic board with temperature sensor, antenna, status LED and replaceable button cell battery

Felt: hygroscopic polymer with preservative to prevent albumin degradation. Releases urine on centrifugation with 100% albumin recovery.

Activation tab (measurements start after removal)
Unpack the envelope. Do the test on a Monday, Tuesday, Wednesday or Thursday morning.

Unscrew the cap from the tube and grasp the yellow stick with felt.

On the toilet: first pee for 1-2 seconds. Then pee on the felt for 3 seconds.

Put the yellow stick with the felt in the tube and screw the cap firmly on it.

Place the tube in the plastic bag and close it.

Write the date of the urine test on the back of the plastic bag.

Fill in the consent form (only the first time).

Put the plastic bag (and the consent form) in the return envelope.

Mail the return envelope on the same day that you did the test.

You will receive the result by mail.
THOMAS
Screening method B: “novel”

Foldable urine cup
ACR calibration color board
Urine ACR dipstick
THOMAS
Screening method B: “novel”

1. Unpack the envelope and read the flyer

2. Download the NierCheck app from Google Play or the App Store

3. Open the app and follow the instruction that will appear on your screen

4. After the test you will see the results in the app

5. In case of abnormal results you will receive a letter what to do next
THOMAS
Flow diagram

General population
45 – 80 years
N=15.000

Albuminuria screening
Approach A: PeeSpot test

ACR ≤3.0 mg/mmol

No screening

New hypertension
New diabetes
New hyperlipidemia
New heart failure
New Impaired eGFR

ACR >3.0 mg/mmol

Confirmation

Elaborate screening

Albuminuria screening
Approach B: App ACR test

ACR ≤3.0 mg/mmol

No screening

Confirmation

Elaborate screening

ACR >3.0 mg/mmol

New hypertension
New diabetes
New hyperlipidemia
New heart failure
New Impaired eGFR
Outcomes

- Percentage of the population participating in screening, and their characteristics

- Number of subjects identified with newly discovered:
  - Increased albuminuria
  - Impaired eGFR
  - Hypertension
  - Diabetes
  - Hypercholesterolemia

- Percentage subjects going to their GP for treatment, and percentage subjects actually receiving treatment

- Cost-effectiveness of screening with respect to ESKD and CVD prevention (modelling actual and ideal scenarios)
Supporting material

- App (now available in Google Play Store and App store)
- Internet site (www.niercheck.nl)
- Information brochures (various languages)
- Flyers (various languages)
- Media campaign (local journals, video GP offices)
Conclusions

• CKD screen and treat programs can improve prognosis, with respect to ESKD and CVD prevention.

• The present screening strategy has been for more than two decades opportunistic, clinic based screening of high risk subjects only
  - What defines high risk patients?
  - Will identification lead to (major) changes in treatment?
  - Why has success been limited?

• Future screening strategies could include:
  - Screening lab registries for progressive CKD?
  - Population screening?

• Screen for eGFR only? Most subjects with low eGFR are known. Screening for eGFR will only lead to late intervention, and at that stage interventions may have less efficacy.
Conclusions

- Population screening for albuminuria may be another option:
  - Most subjects with elevated albuminuria are yet unknown,
  - They have relatively preserved eGFR and are yet not treated, allowing early preventive interventions.
  - Screening can be done at low costs (e.g. home based tests, in combination with other tests).
- Cost-effectiveness studies should incorporate benefits with respect to ESKD, but also CVD prevention.