Challenges of risk-adjusted prevention strategies for breast cancer

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Presentation at JCR, Ispra 2105: Putting science into standards
Personalized risk prediction of breast cancer

Topics

- State of the art in breast cancer heritability
- Research gaps in clinical translation
- Plaedoyer for conjoint actions
Breast cancer genetics as paradigm:

25-40% of common solid tumors are associated with hereditary risk factors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Heritable factors (95% CI)</th>
<th>Heritable and environmental factors (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>27% (4-41)</td>
<td>6% (0-22)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>35% (10-48)</td>
<td>5% (0-23)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>42% (29-50)</td>
<td>0% (0-9)</td>
</tr>
</tbody>
</table>

Lichtenstein et al. NEJM 2000
Contribution of known genetic factors to familial aggregation of breast cancer

Unexplained: 50%

Additional variants – iCOGS estimation
Common variants - iCOGS
Common variants - pre-iCOGS
TP53
PTEN
LKB1
CHEK2
ATM
PALB2
BRIP1
XRCC2
BRCA1
BRCA2
1. ExSeq
2. Case/ctr

- Risk factors define risk continuum
- Personalised risk prediction
Clinically important: Genotype/phenotype correlation

- Genotype determines phenotype and clinical disease course
- Genotype relevant for clinical decision on the uptake of preventive measures

*Meindl et al. Nat. Genet 2010
Gevensleben et al. submitted
Use of and Mortality After Bilateral Mastectomy Compared With Other Surgical Treatments for Breast Cancer in California, 1998-2011

Allison W. Kurian, MD, MSc; Daphne Y. Lichtensztajn, MD, MPH; Theresa H. M. Keegan, PhD; David O. Nelson, PhD; Christina A. Clarke, PhD; Scarlett L. Gomez, PhD

JAMA. 2014;312(9):902-914. doi:10.1001/jama.2014.10707

N=189 734 pts
Office of public health genomics (OPHG) of the CDC, ACCE Eurogentest, harmonization of genetic testing in Europe

AET: Translation of genetic test into public health programs

ACCE Model
• Analytic validity
• Clinical validity
• Clinical utility
• Ethical, legal and social implication
## Suggested conjoint actions on the EU level

<table>
<thead>
<tr>
<th>Actions items</th>
<th>Deliverables</th>
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<tbody>
<tr>
<td>Consolidate and cross-link <strong>quaternary care centers</strong> for familial cancers</td>
<td><strong>Standards</strong> in counseling, genetic testing and clinical interpretation</td>
</tr>
<tr>
<td>Establish <strong>familial cancer registries</strong> incl. genetic databases (prerequisites for the interpretation of genetic test results)</td>
<td>Evidence-based preventive measures (<strong>prospective cohorts</strong>)</td>
</tr>
</tbody>
</table>
| Provide **educational programs** to improve genetic and preventive literacy of doctors and persons at risk | **Quaternary prevention:**  
  - Avoid over-prevention,  
  - Secure preference-sensitive shared decision making                                         |
| Define **rights and obligations** for the uptake of risk-adjusted prevention   | **Distributive justice** in prevention                                                                                                        |
### Implementation facilitators

<table>
<thead>
<tr>
<th><strong>Tools</strong></th>
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<tr>
<td><strong>Checklist</strong> of inclusion criteria for the offer of genetic counseling and testing</td>
<td></td>
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<tr>
<td>Harmonized and culture-sensitive <a href="#">information resources</a> for counselees and counselors</td>
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<tr>
<td>Patient/Counselee <a href="#">decision aids (PtDA)</a> to allow for preference-sensitive shared decision making</td>
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<tr>
<td>Validated instruments for the identification of <a href="#">psycho-social burden</a> (e.g. HADS)</td>
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</table>
RiskAp initiative funded by the German Ministry of Health 2015

- Intern. and interdisciplinary experts group
- Framework for risk-adjusted prevention strategies on a meta-level
- Based on the position paper on risk-adjusted prevention of the National Cancer Plan
- Associated to CanCon WP9 on the organization, governance and evaluation of cancer screenings
Thanks to......

The Consortium

The German Cancer Aid

The BRCA-Network
Thank you very much for your attention

Cologne Cathedral with Gerhard Richter windows
Back-Up‘s for discussion (not for publication!)
Almost 40 years ago, WHO commissioned a report on screening from James Maxwell Glover Wilson, then Principal Medical Officer at the Ministry of Health in London, England, and Gunnar Jungner, then Chief of the Clinical Chemistry Department of Sahlgren’s Hospital in Gothenburg, Sweden. The report, published in 1968, was entitled *Principles and practice of screening for disease* and it has since become a public health classic.

Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years

Anne Andermann, Ingeborg Blancquaert, Sylvie Beauchamp & Véronique Déry


Box 2: Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Although genetic services and screening programmes aim to improve the health of the population, there is growing concern that the increasing number of genetic tests becoming available at lower costs could compromise the viability of the health care system. Even though the tests themselves may be inexpensive and suitable for large-scale use, the infrastructure and human resources needed to provide appropriate education, counselling, interventions and follow-up are likely to be far more costly. When it comes to the allocation of consumers, the decisions to develop, implement and continue to fund genetic screening programmes are political. On the one hand, governments...
Central Results of the previous pilot study (n=163 BRCA1/2 mutation carriers)

- HADS-Scores

- No significant differences between healthy and affected women
- Higher anxiety scores in BRCA carriers compared to gen.pop.
- Decrease of anxiety scores after 6-8 months independent of chosen preventive measure (iFE or pMTX)
- No significant differences of HADS-Depression over time

Clinical relevant anxiety-scores (>10)

<table>
<thead>
<tr>
<th>Moment of Testing</th>
<th>Numbers</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Before getting the test results</td>
<td>28 von 149</td>
<td>18,8</td>
</tr>
<tr>
<td>6-8 weeks later</td>
<td>44 von 164</td>
<td>26,8</td>
</tr>
<tr>
<td>6-8 months after test results</td>
<td>18 von 100</td>
<td>18,0</td>
</tr>
<tr>
<td>Female German Population</td>
<td></td>
<td>7,4</td>
</tr>
</tbody>
</table>

*Means of the German female population, Hinz and Schwarz, 2001
Central Results of the previous Study MoreRisk 2: Anxiety-scores correlate significantly with the intention to have pMTX or join the iFE 6-8 weeks after getting the test results.

- 52.4% of women with increased anxiety-scores have had pMTX 6-8 months after getting the test results.
- 73.8% of women with normal anxiety-scores join the iFE 6-8 months later.

P<0.001 Pearson Chi²-Test
Further steps

<table>
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<tr>
<th>Explore requirements for preference sensitive decisions</th>
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<tbody>
<tr>
<td>Validated instruments for the identification of <strong>psycho-social burden</strong></td>
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<tr>
<td>Explore if <strong>psycho-social intervention</strong> has an effect on anxiety levels and decision on preventive measures?</td>
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<td>Provide culture-sensitive <strong>information resources</strong> for counselees and counselors</td>
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<td>Develop patient/Counselee <strong>decision aids (PtDA)</strong></td>
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<td>Increase <strong>genetic and preventive literary</strong> of doctors and patients</td>
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</table>
| ➢ Complement **EBM** by narrative-based medicine (**NBM**)  
➢ Ensure quaternary care, i.e. avoid over-prevention |