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IMPLEMENTING NATIONAL SCALE OPPORTUNISTIC SCREENING OF BIOBANK SAMPLES FOR PERSONALISED CANCER PREVENTION

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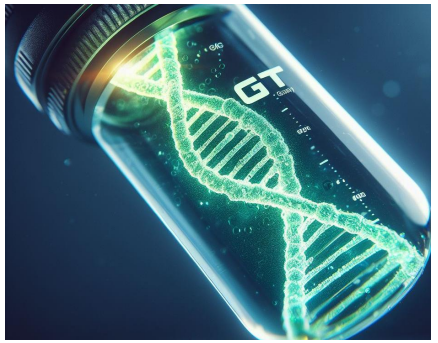
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GENOME HEALTH PILOT - A MODEL FOR TRANSFERRING BIOBANK FINDINGS TO SAMPLE DONORS AND HEALTH CARE. WHAT AND WHY?

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FINNGEN

- FinnGen (finngen.fi/en) has produced >500 000 genotypes from Finnish biobank samples and returned this information to biobanks



- > 95% of donors wish to be contacted to receive research findings relevant for their health

- CAN THE RETURNED GENOTYPES BE UTILISED IN HEALTH CARE AND WHAT ADDITIONAL MEASURES WOULD THIS REQUIRE?



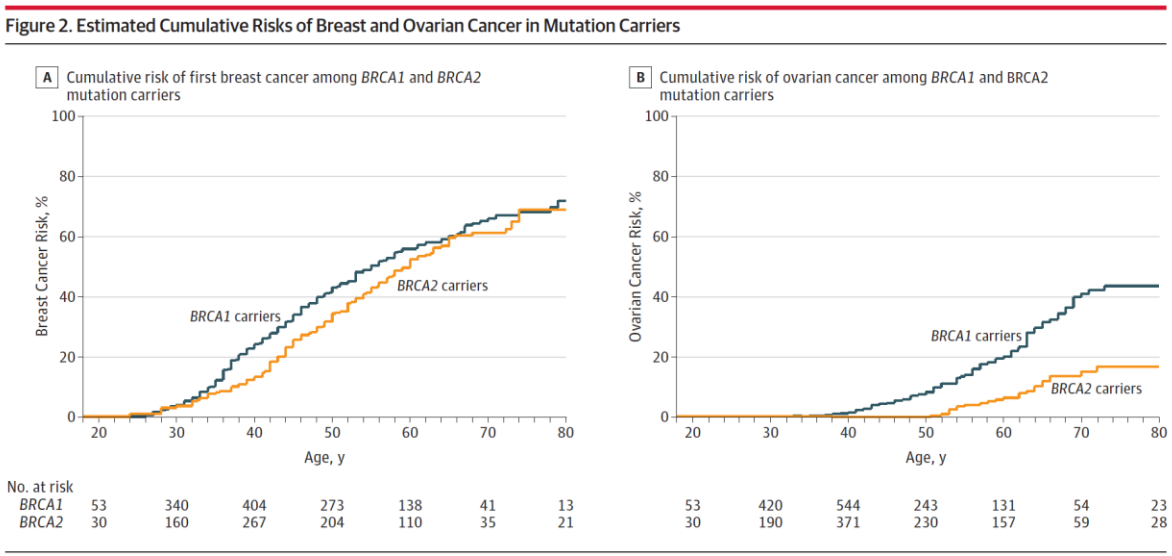
GOALS OF THE *GENOME HEALTH* PILOT

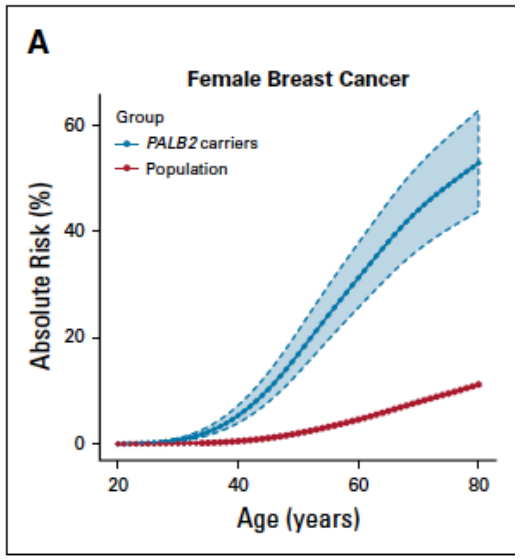
- Can we identify risk allele carriers from FINNGEN genotyping data returned to biobanks?
  - If so, do we identify individuals, who are unaware of their carrier status?
- Can we build a national plan for returning genetic data to health care?
  - Technical and analytical requirements
  - The path should be applicable to all hospitals, follow legal requirements and be acceptable by all stakeholders
- What are the attitudes of biobank donors receiving genetic information?
- Would such opportunistic screening be cost-effective?

- *Joint project of all 6 Finnish hospital biobanks.*

THREE GENES WITH SIGNIFICANT CANCER RISK (*BRCA1, BRCA2, PALB2*)

- *BRCA1* and *BRCA2* genes are included in ACMG recommendations on reportable secondary genetic findings from clinical sequencing
  - French SFMPP (*The French Society of Predictive and Personalized Medicine*) includes, in addition to *BRCA*-genes, also pathogenic variants of *PALB2*
- The selected genes represent high risk cancer-predisposing variants that exist in the Finnish population; predisposing to at least breast, ovarian and prostate cancer
  - There is **a clear model of action** and **treatment recommendations** (screening, preventive surgery, targeted drugs *e.g.* PARP inhibitors)
  - 28 *BRCA1* variants, (freq 1:1000); 18 *BRCA2* variants, (freq 1:1000); 1 *PALB2* founder variant, (freq 1:600)





Kuchenbaecker et al. *JAMA*. 2017

Mars et al. *Nat. Comm*. 2020

GENOME HEALTH PILOT RESULTS:

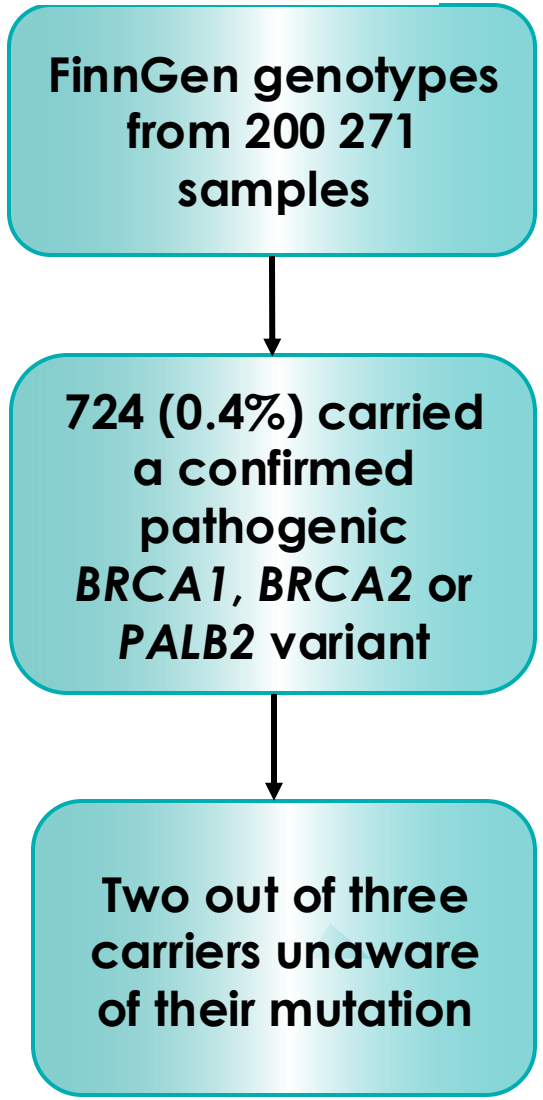
Suspected pathogenic variant carriers were first identified from raw genotyping data

- Results validated with an NGS-based method in clinical laboratory
- Around 1 % of samples sent for validation

Positive predictive value in identification of rare variants increases when a larger number of reference samples are available for variant calling

The positive predictive value varies between SNP markers

GENE	DF4 (~64 000 samples): Confirmed % (n)	DF9 (~136 000 samples): Confirmed % (n)	Confirmed DF1-DF9 (n)
BRCA1	**21 %** (50)	**90 %** (36)	86
BRCA2	**14 %** (31)	**62 %** (100)	131
PALB2	**100 %** (193)	*(314)	507
*not validated			**724**



BIOBANK

1. Identify potential carriers of pathogenic variants

Appr. 0.4 -1% are potential carriers

2. Identify sample donors

3. Internal validation with diagnostic NGS-method

BRCA1/BRCA2/PALB2 mutation carriers

4. Recontacting of confirmed carriers

HEALTH CARE

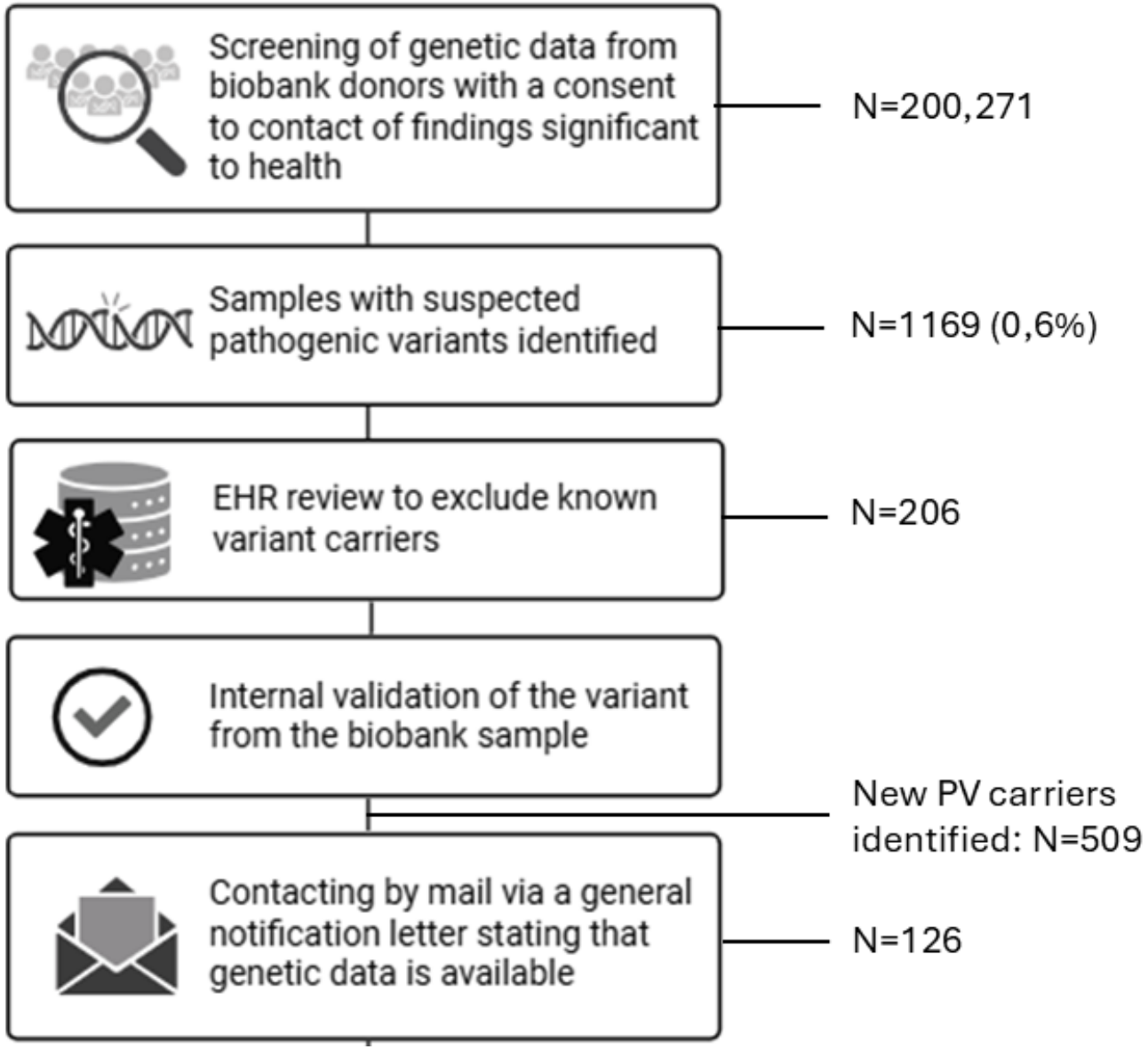
5. Mutation confirmation from a new sample

6. Genetic counseling

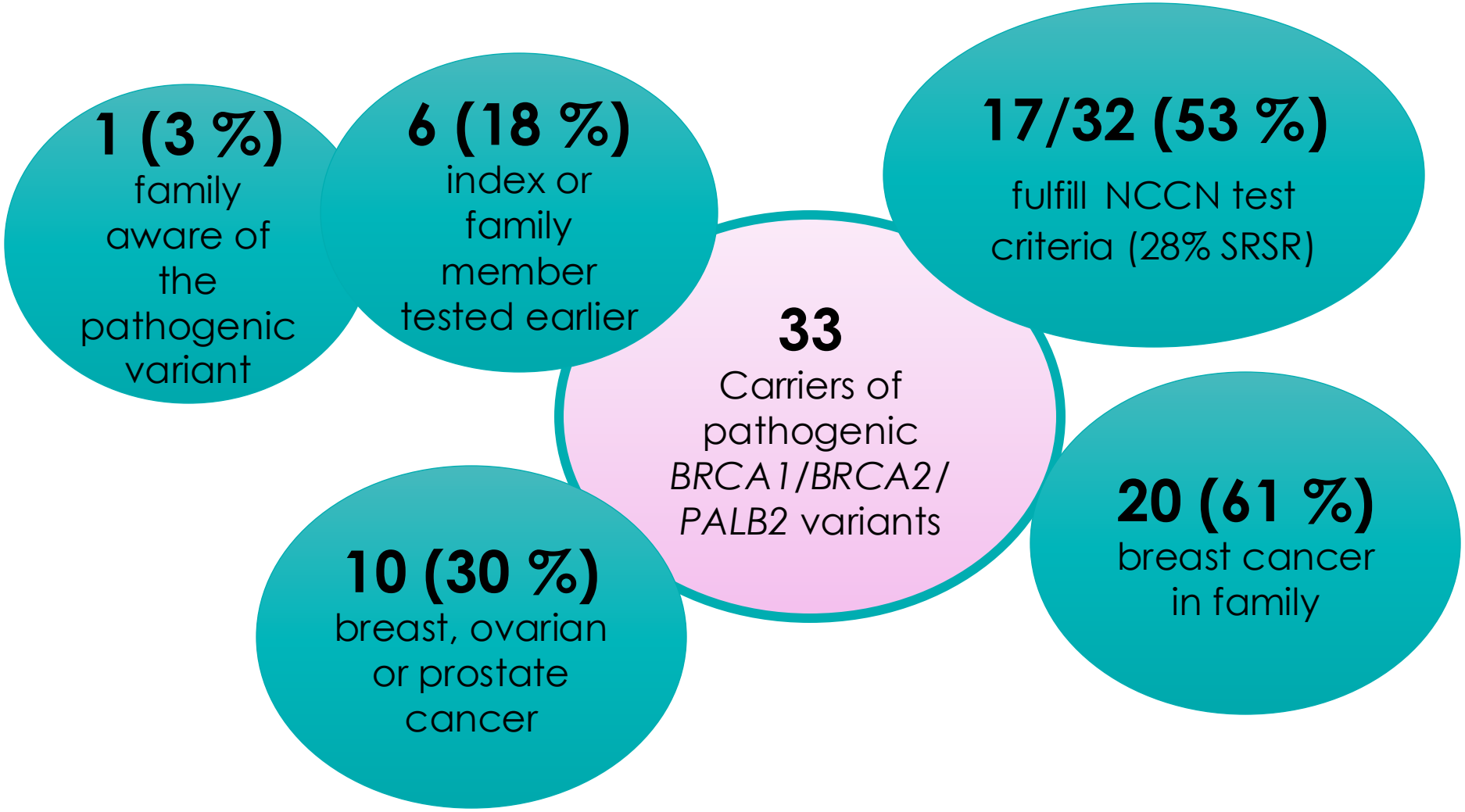
7. follow-up / preventive surgery

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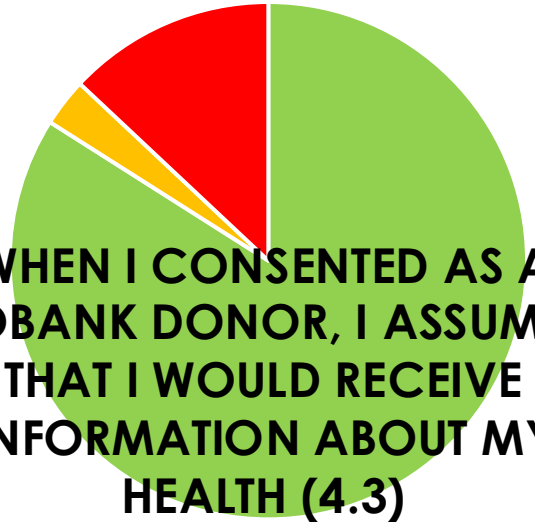

Screening of genetic data from biobank donors with a consent to contact of findings significant to health
N=200,271
Samples with suspected pathogenic variants identified
N=1169 (0,6%)
EHR review to exclude known variant carriers
N=206
Internal validation of the variant from the biobank sample
New PV carriers identified: N=509
Contacting by mail via a general notification letter stating that genetic data is available
N=126
User authentication and portal login for written counselling materials
Possibility to give approval to receive genetic results from biobank sample
Disclosure of findings through telecounselling
N=66
Survey responders: N=47
Referral to genetics department for confirmatory genetic testing
Genetic counselling
Follow-up and care

CLINICAL RELEVANCE OF THE FINDINGS (SUBGROUP)

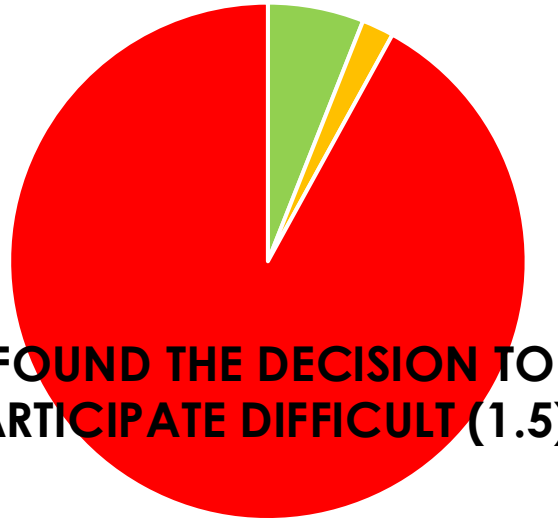


Clinical information by: Eveliina Salminen

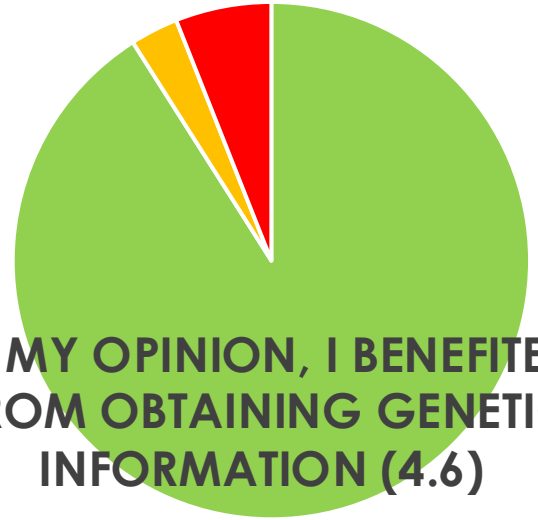
BIOBANK DONORS' ATTITUDES ON RECEIVING GENETIC INFORMATION:



WHEN I CONSENTED AS A BIOBANK DONOR, I ASSUMED THAT I WOULD RECEIVE INFORMATION ABOUT MY HEALTH (4.3)

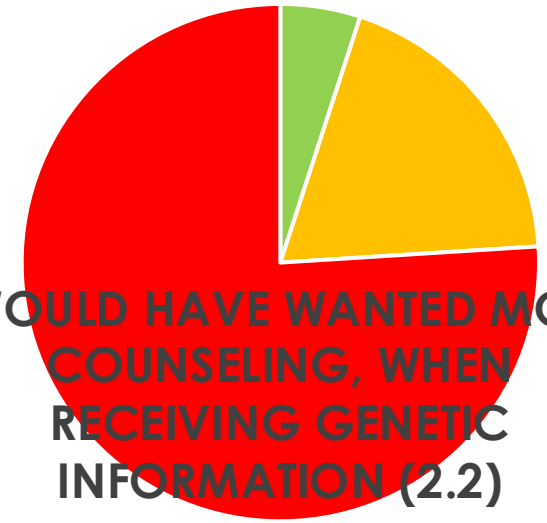


I FOUND THE DECISION TO PARTICIPATE DIFFICULT (1.5)



IN MY OPINION, I BENEFITED FROM OBTAINING GENETIC INFORMATION (4.6)

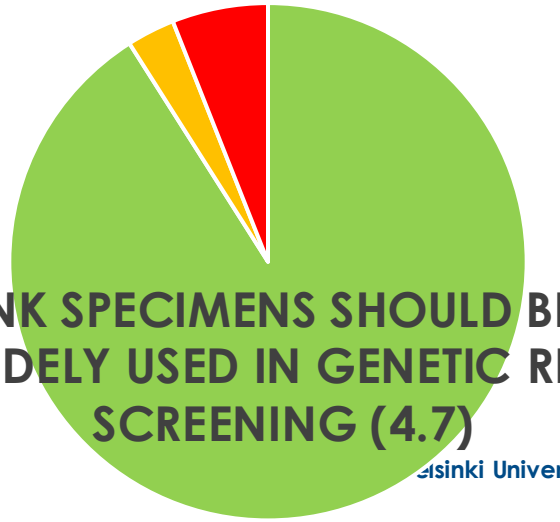
AGREE (4-5)
NEUTRAL (3)
DISAGREE (1-2)



I WOULD HAVE WANTED MORE COUNSELING, WHEN RECEIVING GENETIC INFORMATION (2.2)



I REGRET MY DECISION TO PARTICIPATE (1.7)



BIOBANK SPECIMENS SHOULD BE MORE WIDELY USED IN GENETIC RISK SCREENING (4.7)

COST-EFFECTIVENESS ANALYSIS

OBJECTIVE
Feasibility and cost-effectiveness of returning validated genetic cancer risk information to female sample donors

ANALYSIS **EE345**
Cohort simulation of women 20-79 years old with mutations associated with breast and ovarian cancer: compare recall to no recall over lifetime horizon

ESIOR

KNOWLEDGE GAINED
Recall was cost-effective for women with *BRCA1* and *BRCA2* variants aged 20-79 years, and with *PALB2* variants aged 30-59 years. Inclusion of relatives improved the results further

KEY MESSAGE
Returning genomic information to sample donors resulted in noteworthy health gains and was feasible and cost-effective

Lifetime Cost-Effectiveness of Hereditary Breast and Ovarian Cancer Prevention based on FinnGen and Biobank Data, Data Returning Process, and Prophylaxis

Soini E[1], Asseburg C[1], Jalkanen K[1], Pehrsson M[2], Lundström T[1], Meretoja T[3], Hautalahti M[4], Salminen E[5], Auranen A[6], Mäkelä J[4], Carpén O[7]

METHODS

The methods of the economic evaluation are summarized in the table below using the PICOSTEPS framework.[3]

COMPONENT	CONTENT
Patients	Women with germline mutations (*BRCA1/2*, *PALB2*) conferring **high risk of HBOC**, aged 20-79 years
Intervention	Recall by Helsinki Biobank, resulting in prophylactic interventions, intensified screening, or no change
Comparator	No recall
Outcomes	Number of HBOC cases, deaths due to HBOC, costs (euros in 2022), life-years (LY) and quality-adjusted life-years (QALY), and net monetary benefit (NMB) at a low prophylaxis willingness-to-pay (28,245 €/QALY gained)
Setting	**Cost-effectiveness** modelling using a cohort simulation model
Time	**Lifetime**. 3% per annum discounting for life-years, QALYs, and costs
Effects	Prophylactic bilateral mastectomy and risk-reducing bilateral salpingo-oophorectomy **reduce risk of HBOC**
Perspective	Finnish **societal perspective**
Sensitivity analyses	Type of mutation, age group, impact of relatives

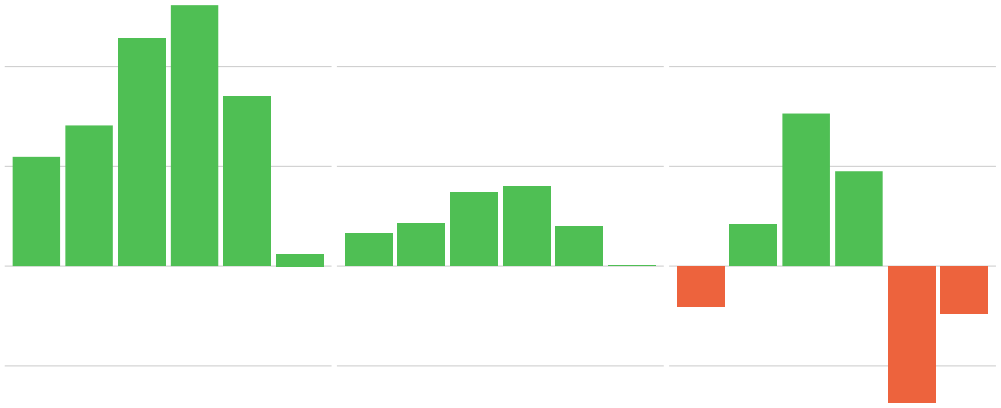


Figure 3. Expected discounted lifetime net monetary benefit by mutation and age.

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CONCLUSIONS

Screening of FINNGEN genotypes enriches probability for identifying *BRCA1-2/PALB2* mutation carriers by **200-fold**

Genomic information returning to biobanks can be used to identify individuals with significant cancer risk

In our cohort 67% of the carriers had no information about their carrier status in medical records

Biobank donors in Finland support the return of clinically meaningful health information

This approach is cost effective and could serve as a model for opportunistic preventive screening also for other diseases with high genetic risk

ACKNOWLEDGEMENTS

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