Our Common Future

Hannover · Essen
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VolkswagenStiftung · Deutsche Messe Hannover · Germany · Stiftung Mercator · Landeshauptstadt Hannover · RUHR.2010

Can we predict cancer risk ? –

monogenic versus complex traits

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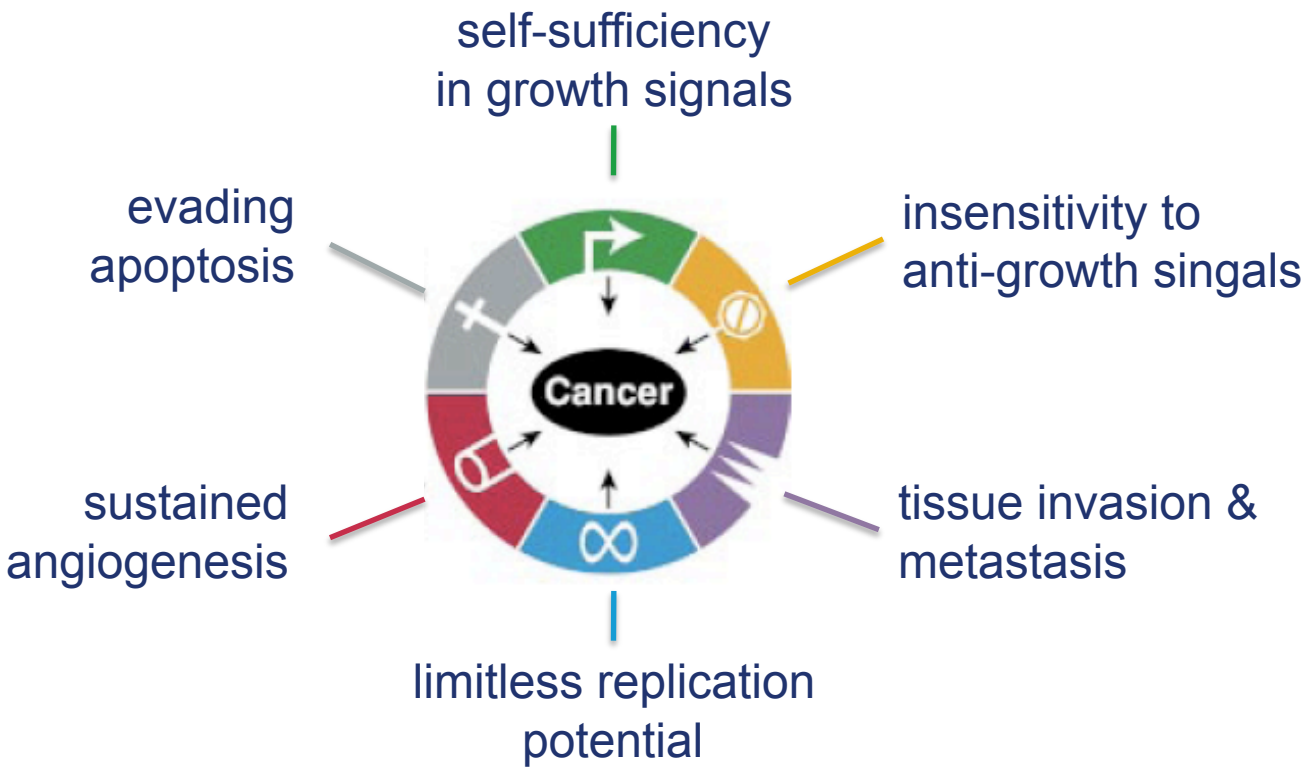
Overview

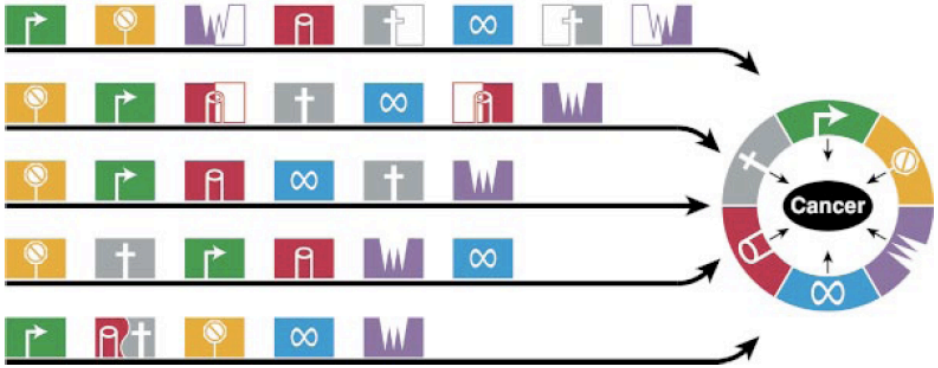
- introduction
- clinical utility managing hereditary cancer syndromes
- tasks in counselling cancer families
- summary

The hallmarks of cancer



adapted from Douglas Hanahan and Robert A. Weinberg, Cell 100 (2000)

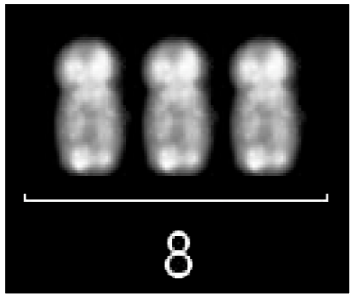
Cancer – a multistep process



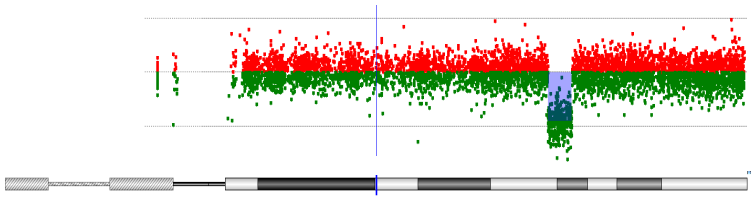
" While we believe that virtually all cancers must acquire the same six hallmark capabilities, their means of doing so will vary significantly, both mechanistically and chronologically."

adapted from Douglas Hanahan and Robert A. Weinberg, Cell 100 (2000)

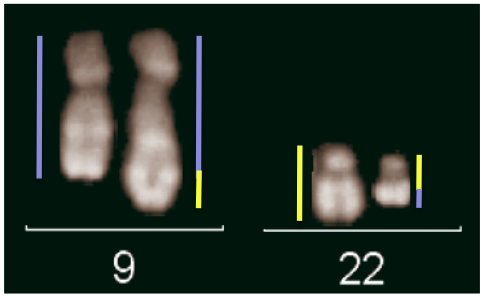
Genetic aberrations in cancer cells



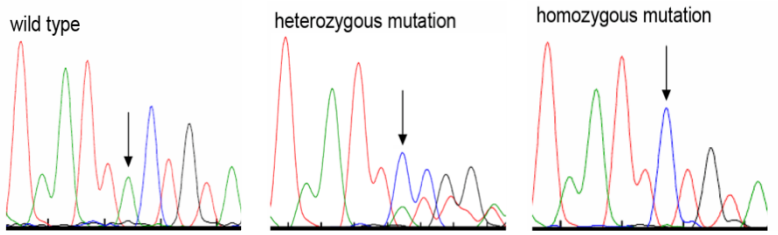
gains



losses

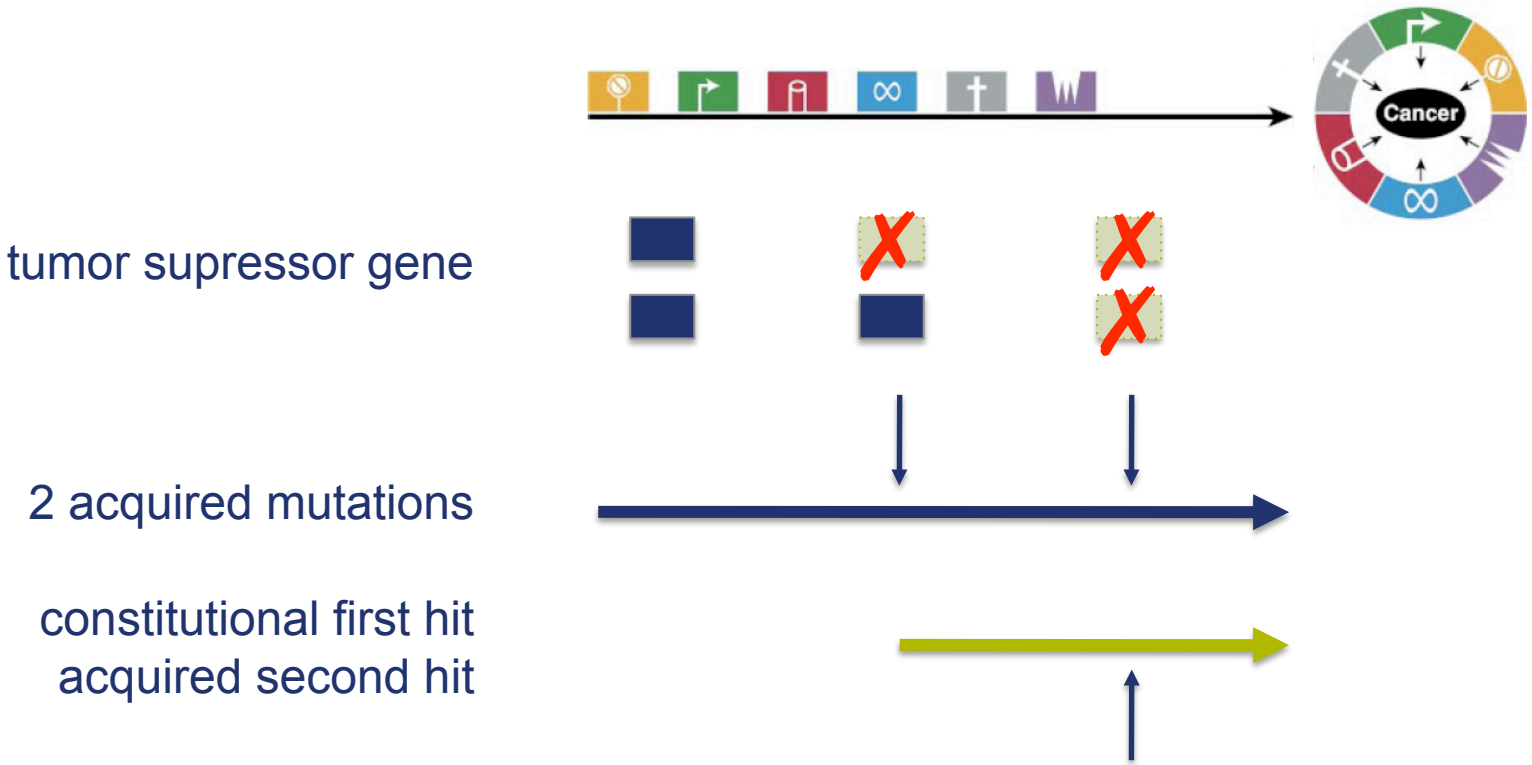


translocations



point mutation

Acquired or constitutional aberration ?



Familial predisposition to cancer

"a short trip to cancer"

family history

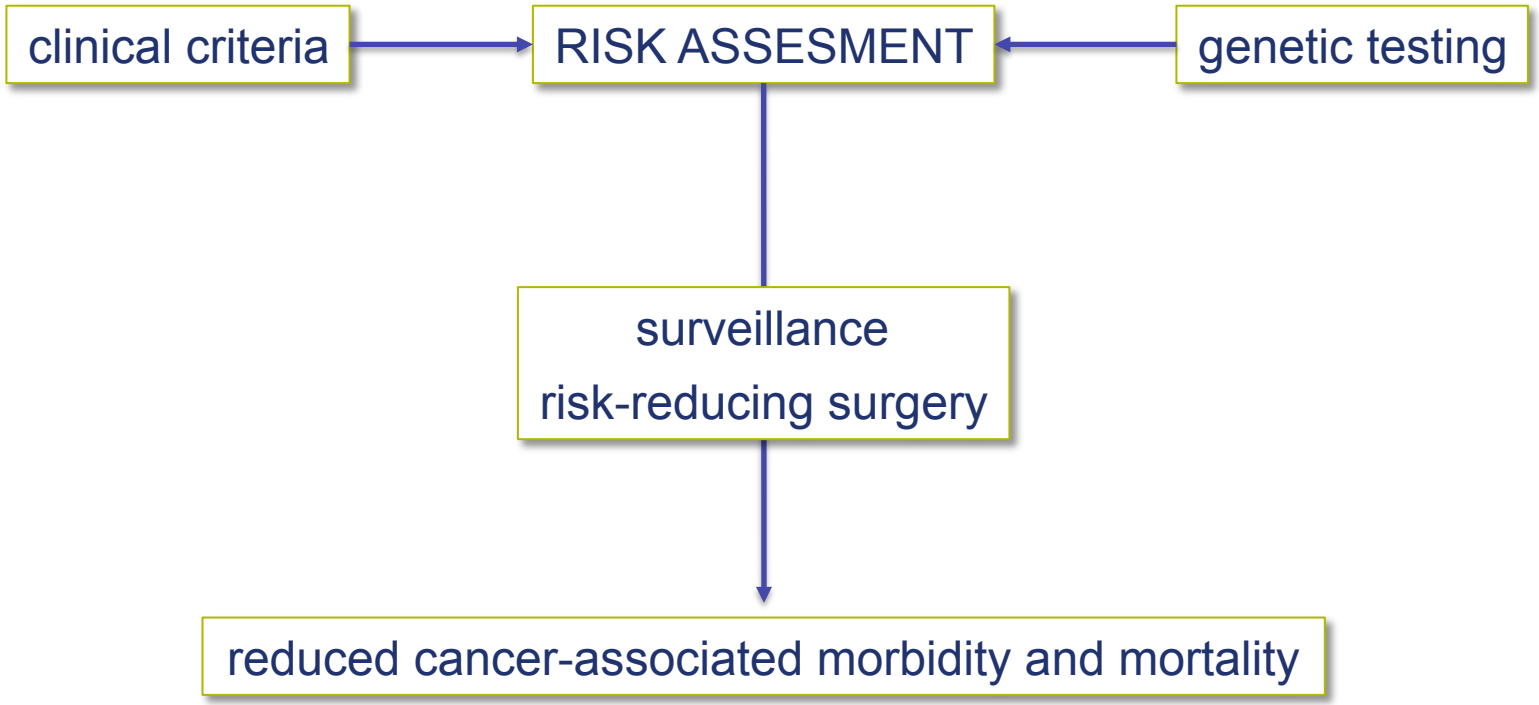
- many cancer patients
- early onset of cancer
- multiple diseases in one individual

Can we predict cancer risk ?

Why do we need to predict cancer risk ?

Can we predict cancer risk ?

Cancer risk prediction & our common future



- well established monogenetic traits

  e.g. hereditary non-polyposis colorectal cancer (HNPCC)

- novel monogenetic traits

  e.g. familial plateld disorder with propensitiy to myeloid malignancy (FPDMM)

- complex traits

  e.g. common low penetrance SNPs associated with familial breast cancer

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Hereditary non-polyposis colorectal cancer

- 3-5% of colorectal cancer
- heterozygous germline mutation in mismatch repair genes
- increased life-time risk for

Colorectal cancer (men)	28–75%
Colorectal cancer (women)	24–52%
Endometrial cancer	27–71%

Ovarian cancer	3–13%
Gastric cancer	2–13%
Urinary tract cancer	1–12%
Brain tumour	1–4%
Bile duct/gallbladder cancer	2%
Small-bowel cancer	4–7%

Vasen et al. J Med Gen 2007

HNPCC – criteria & surveillance

- clinical criteria (Amsterdam/Bethesda guidelines)
- genetic screening
- defined surveillance programs:

  e.g. periodoc examination by colonoscopy

  → detection of early stage tumors
  → reduces colorectal cancer morbidity, and
  → significant reduction of colorectal cancer associated mortality

Vasen et al. J Med Gen 2007

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Novel monogenic traits, e.g. FPDMM

familial **p**lateled **d**isorders with propensity to **m**yeloid **m**alignancies

- heterozygous *RUNX1* germline mutations,
- incomplete penetrance, variable expressivity,
- bleeding history due to low platelets or platelet dysfunction
- MDS/ AML in 1-3 of 5 affected individuals

Novel monogenic traits, e.g. FPDMM

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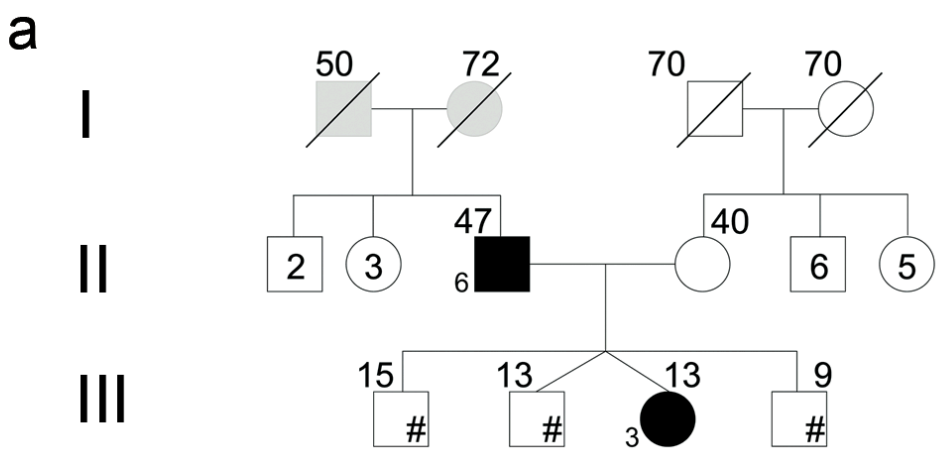

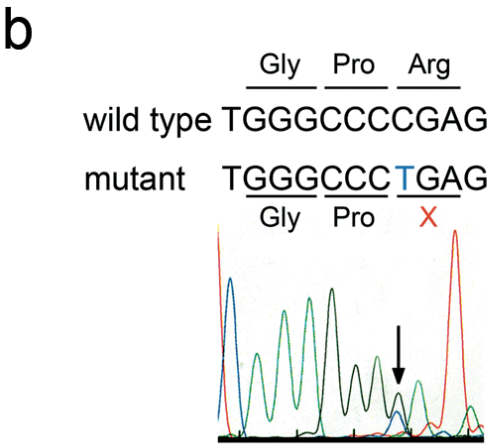

Ripperger et al. Leukemia 2009

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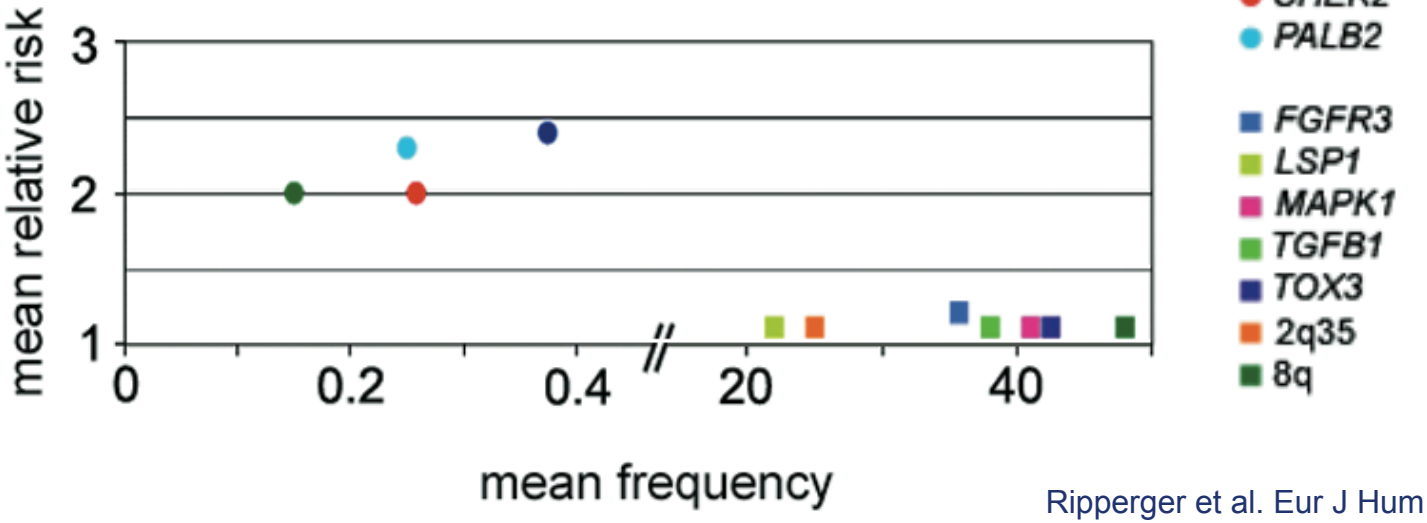
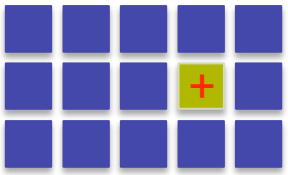
Familial breast cancer

20-40% of affected families
10-fold increased relative risk



Ripperger et al. Eur J Hum Gen 2009

Monogenic vs. complex traits



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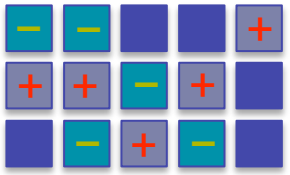
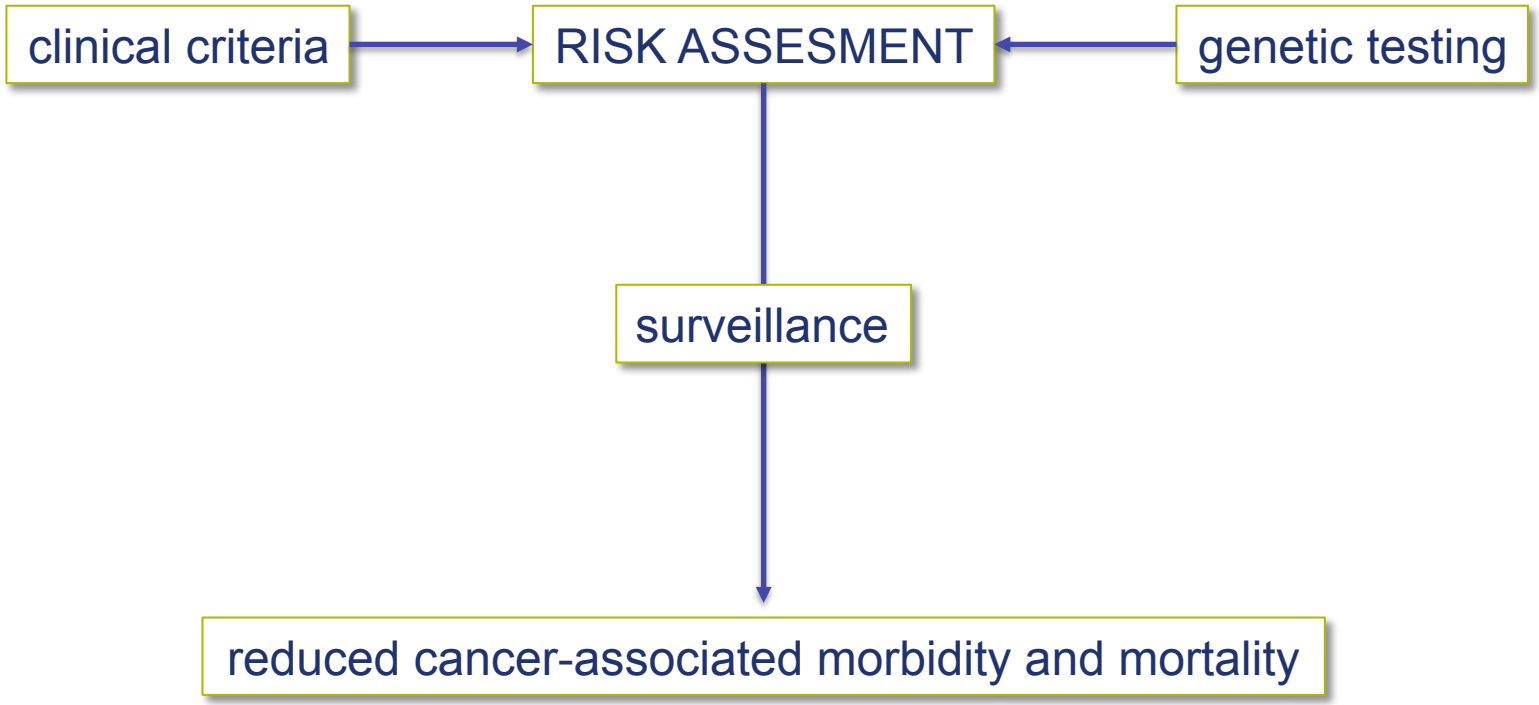


whole set of SNP

risk prediction

models?

Can we predict cancer risk ?



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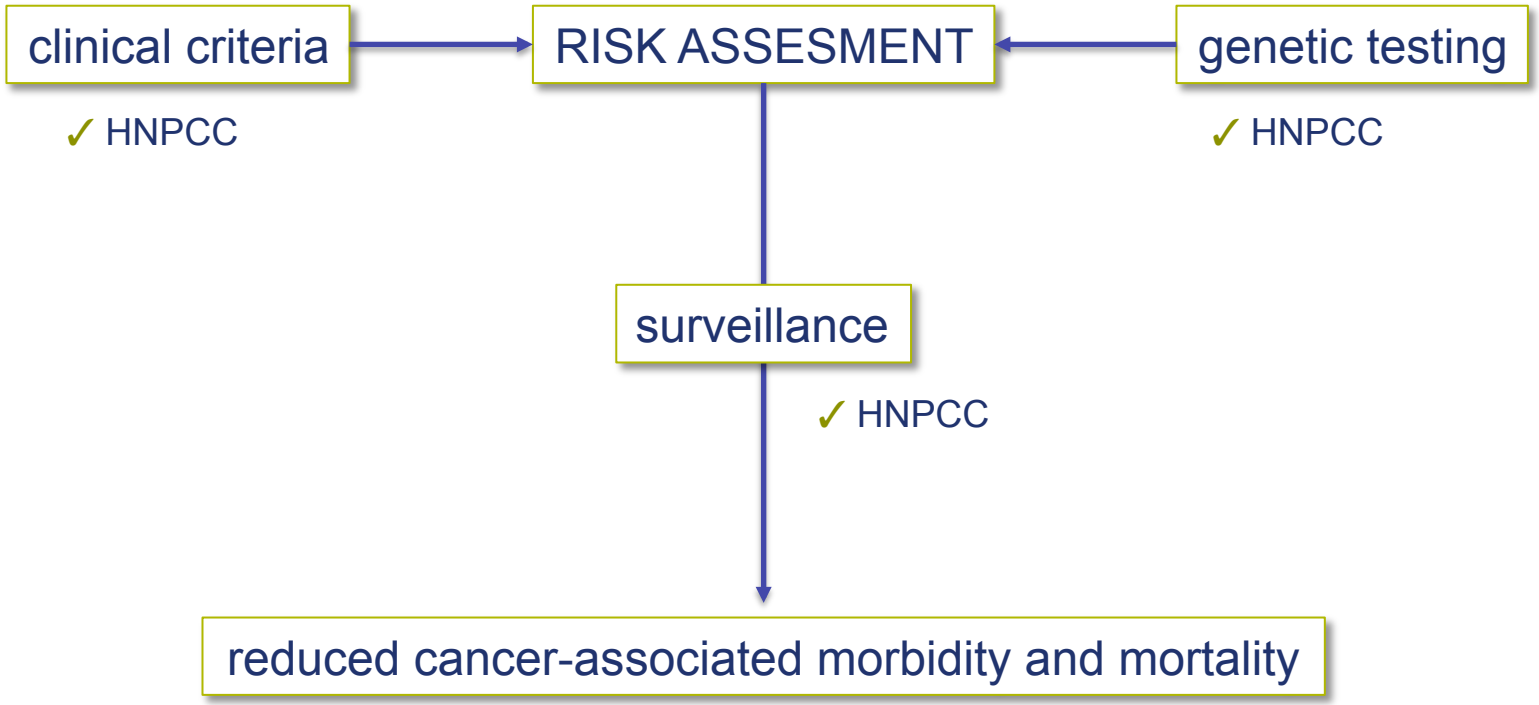

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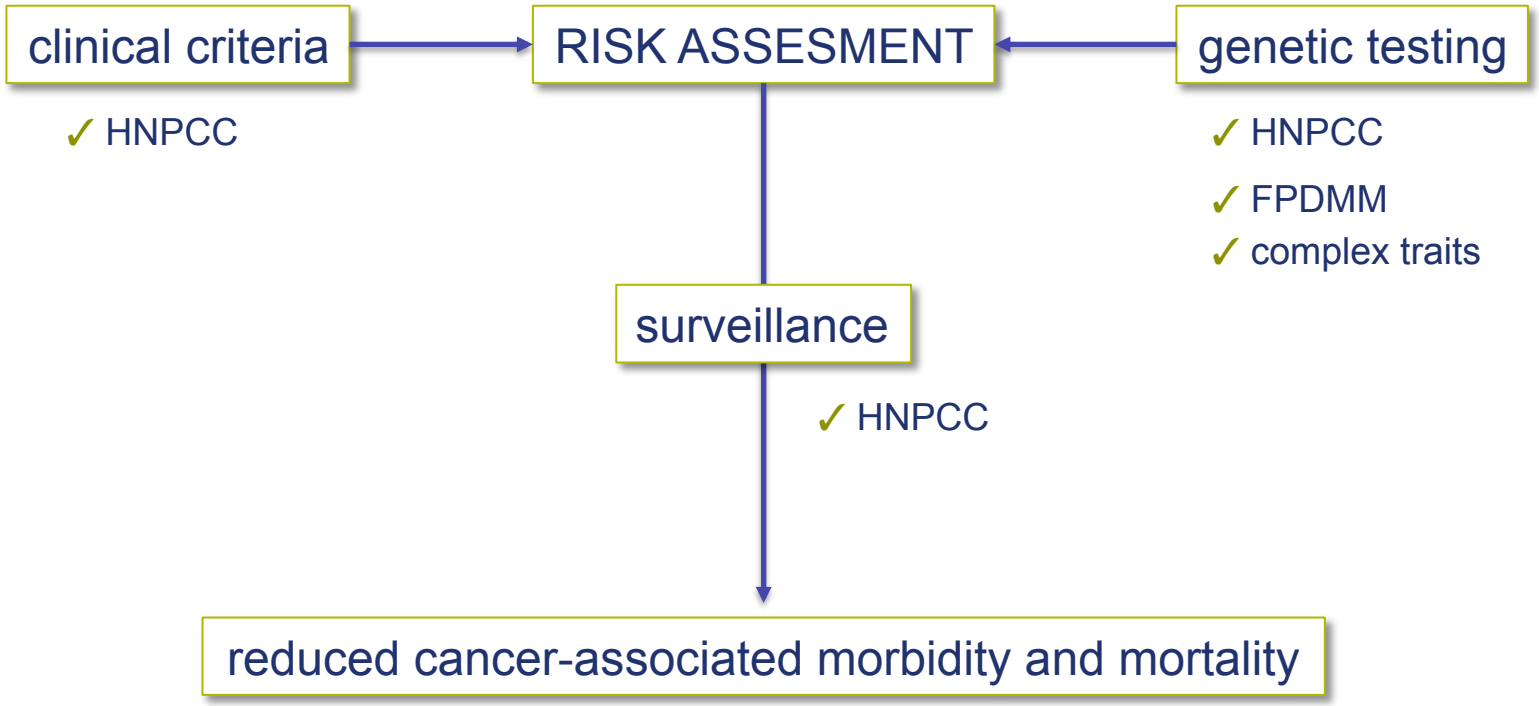

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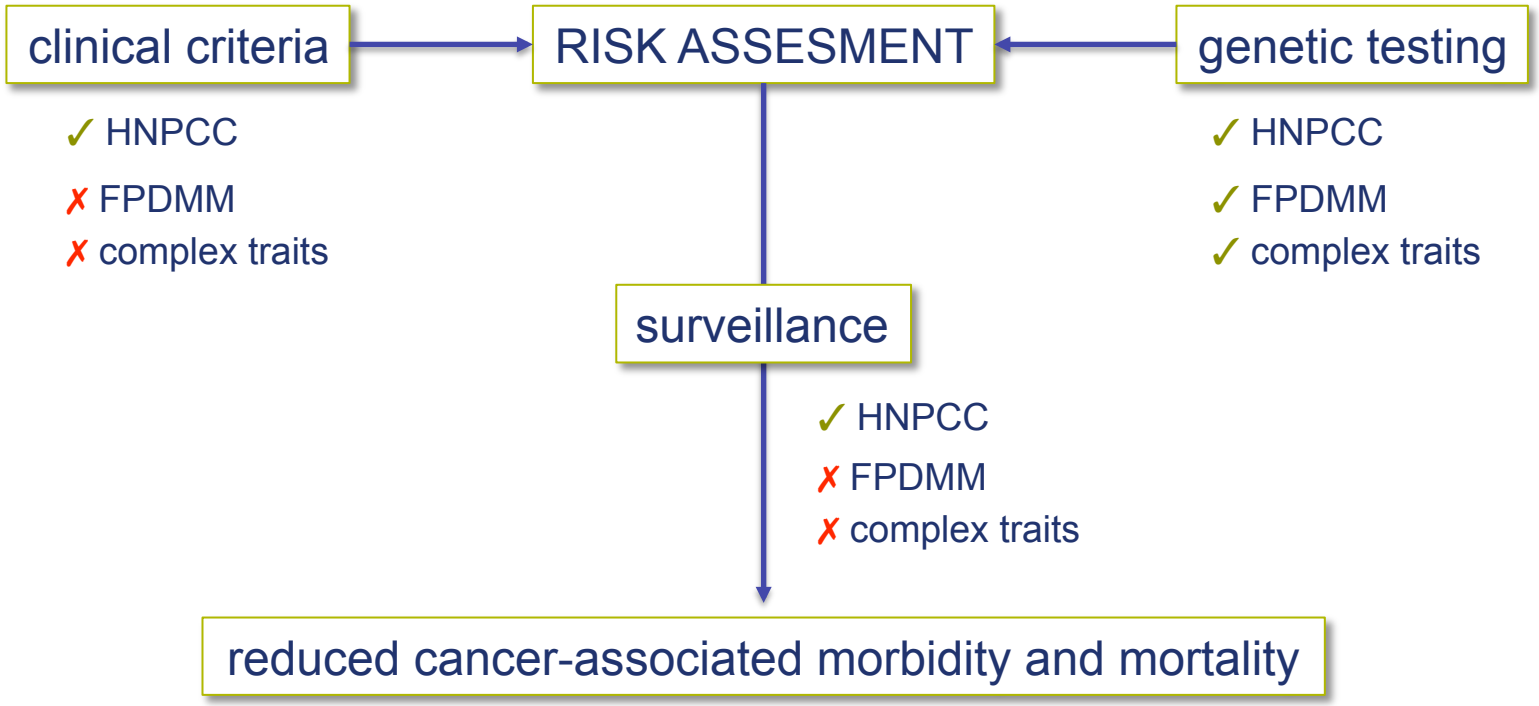
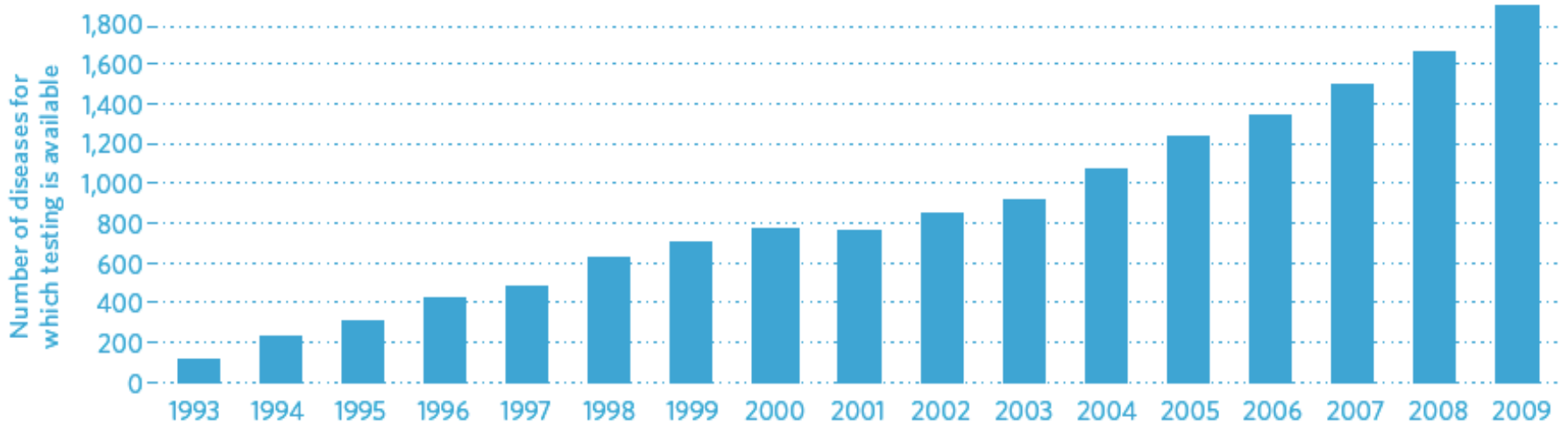


More and more gene tests



Beaudet, Which way for genetic-test regulation?, Nature 466 (2010)

Predicting cancer risk

GENETIC TESTING

CLINICAL VALIDITY

CLINICAL UTILITY

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Volkswagenstiftung