

Population screening: Neonatal screening as an example

Helena Kääriäinen

**National Institute for Health and Welfare,
Helsinki, Finland**

Population screening

- The aim is to detect some individuals who can be offered diagnostics and treatment and thus improve the prognosis of their disease.
- Those with normal result are expected to feel relieved as they were not found to have the condition.
- As a side effect, those involved have to suffer the possible risks, inconvenience and worry created by the screening programme.

WHO criteria for screening

- The condition sought should be an important health problem for the individual and community.
There should be an accepted treatment or useful intervention for patients with the disease.
The natural history of the disease should be adequately understood.
There should be a latent or early symptomatic stage.
There should be a suitable and acceptable screening test or examination.
Facilities for diagnosis and treatment should be available.
There should be an agreed policy on whom to treat as patients.
Treatment started at an early stage should be of more benefit than treatment started later.
The cost should be economically balanced in relation to possible expenditure on medical care as a whole.
Case finding should be a continuing process and not a once and for all project.

Wilson and Jungner 1968

- The condition sought should be **an important health problem** for the individual and community.
- There should be **an accepted treatment or useful intervention** for patients with the disease.
- The natural history of the disease should be adequately understood.
- There should be a latent or early symptomatic stage.
- There should be **a suitable and acceptable screening test or examination**.
- **Facilities** for diagnosis and treatment should be available.
- There should be **an agreed policy on whom to treat** as patients.
- **Treatment started at an early stage should be of more benefit than treatment started later.**
- **The cost** should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case finding should be a continuing process and not a once and for all project.

Newborn screening

- The aim of newborn screening is easily accepted, also among lay people.
 - to detect affected newborns early in order to start treatment and thus **prevent or alleviate** the clinical consequences of the disease
 - as a by-product risk families are picked up and options for family planning and prenatal diagnostics can be offered

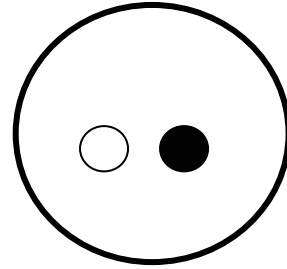
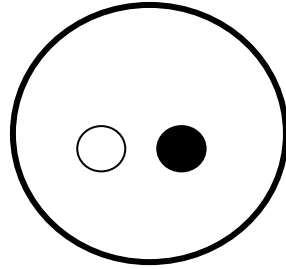
- The condition sought should be **an important health problem** for the individual and community.
- There should be **an accepted treatment or useful intervention** for patients with the disease.
- The natural history of the disease should be adequately understood.
- There should be a latent or early symptomatic stage.
- There should be **a suitable and acceptable screening test or examination**.
- **Facilities** for diagnosis and treatment should be available.
- There should be **an agreed policy on whom to treat** as patients.
- **Treatment started at an early stage should be of more benefit than treatment started later.**
- **The cost** should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case finding should be a continuing process and not a once and for all project.

Newborn screening in Europe

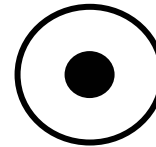
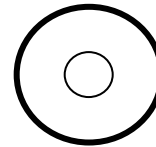
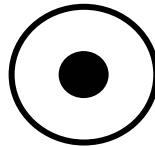
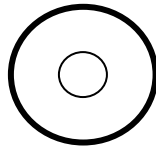
- Usually hypothyreosis
- Usually phenylketonuria (PKU)
- Sometimes a selection of other diseases, usually genetic and inherited as autosomal recessive

Autosomal recessive inheritance

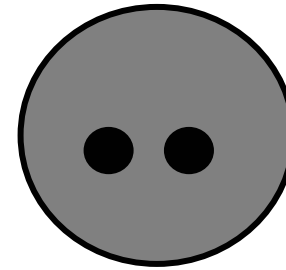
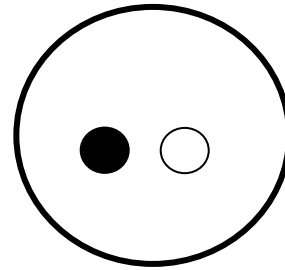
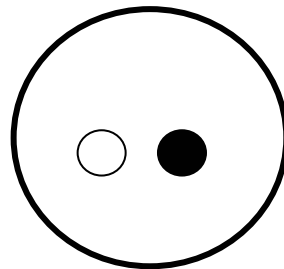
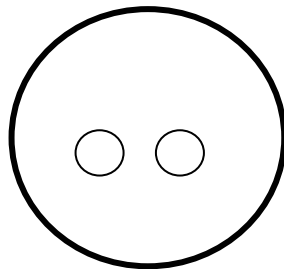
parents



germ cells

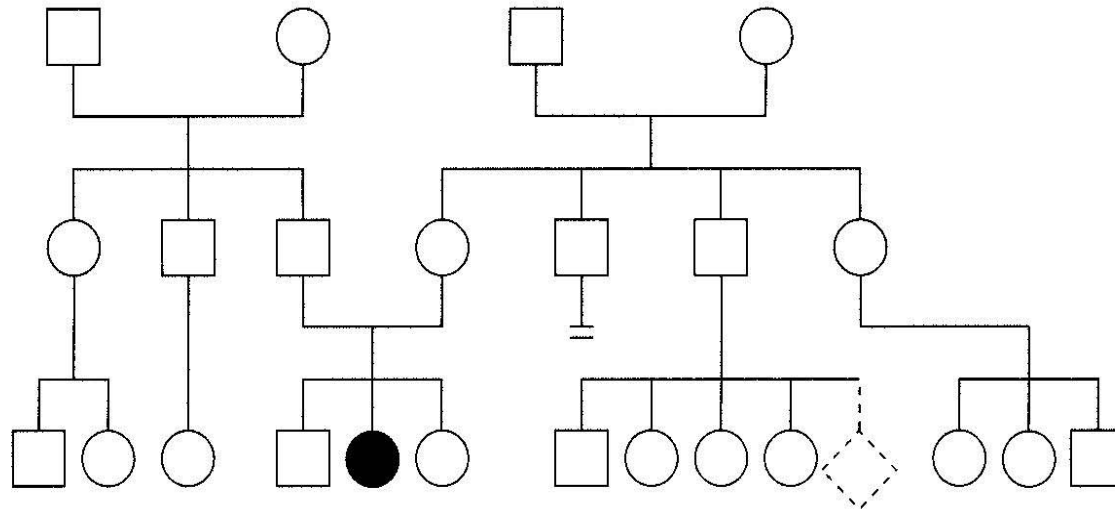
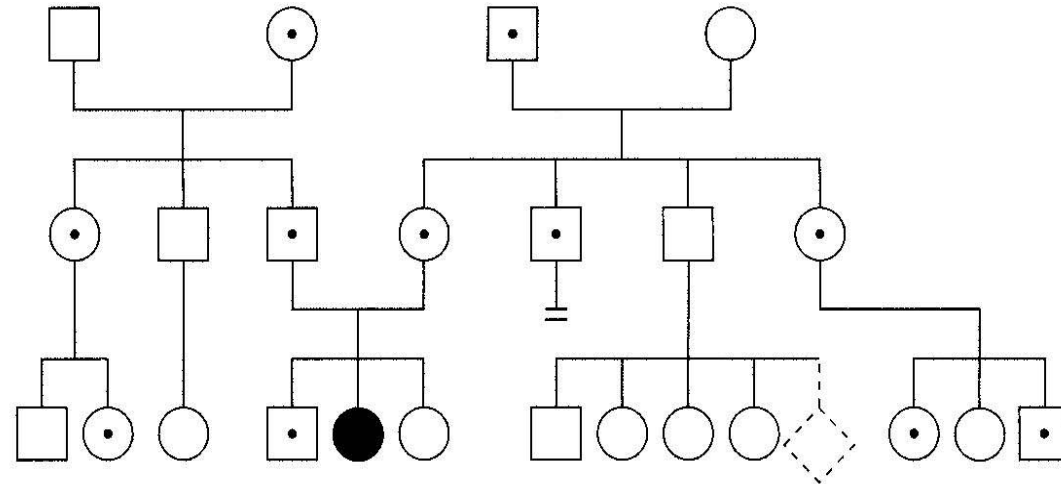


children

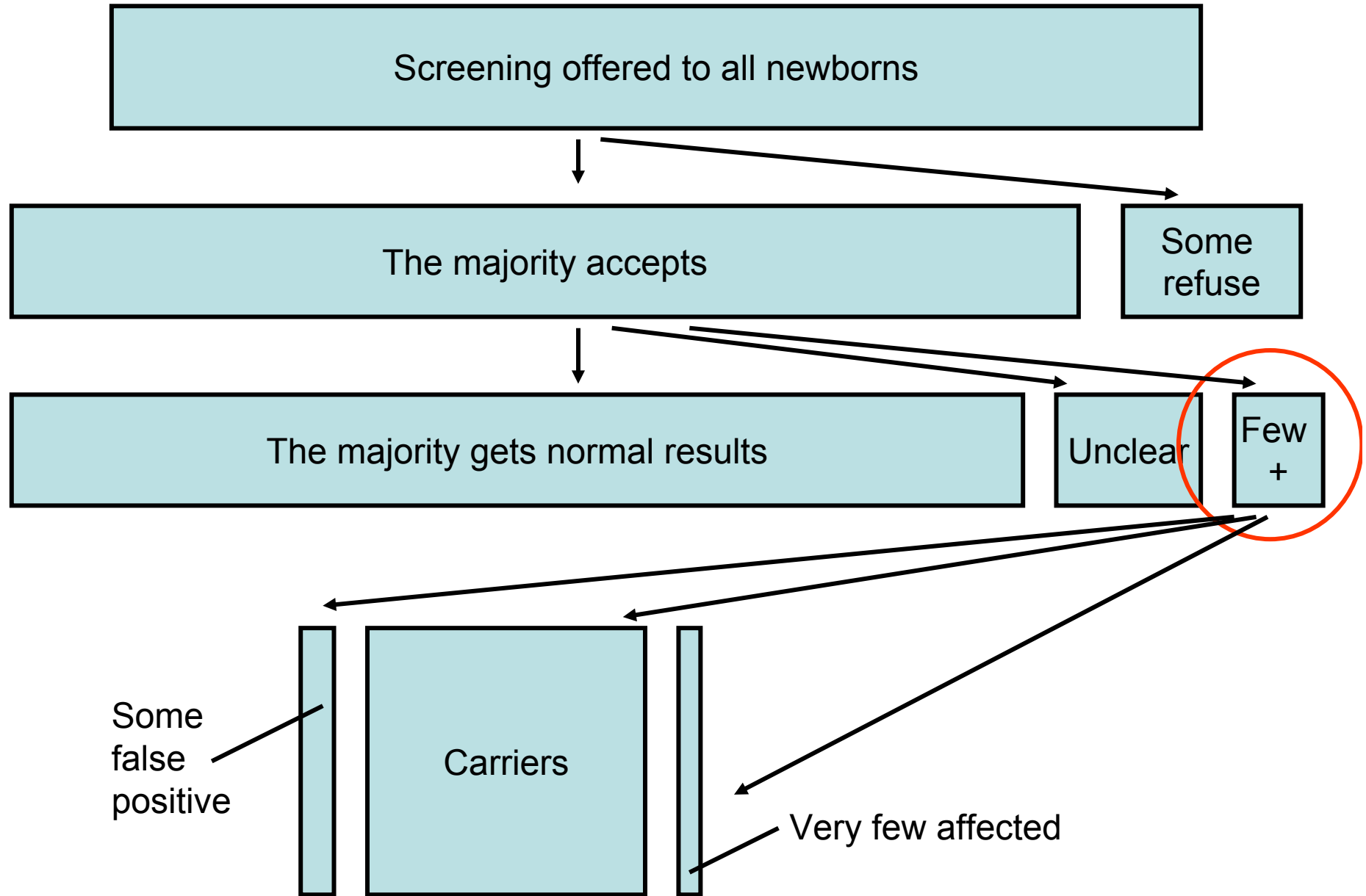


75% healthy

25% affected

A**B**

What happens in newborn
screening?



Screening offered to all newborns

The majority accepts

Some refuse

The majority gets normal results

Unclear

Few +

Some false positive

Carriers

Very few affected

Side effects of newborn screening

- worry caused by the screening
- false positives
- unclear results
- **detecting carriers**
- delayed diagnosis in case of false negatives

Four ethical principles in health care

- Beneficence
 - Non maleficence
 - Respect for autonomy
 - Justice
-
- What is the hierarchy among these principles?

Neonatal screening in Finland

- Only hypothyreosis, from umbilical blood
- PKU screening for couples where both parents are of non-Finnish origin

Newborn screening in Finland

- As newborn screening program in Finland does not allow easy addition of new diseases, a very comprehensive Health Care Technology Assessment project was undertaken to evaluate newborn screening.
 - Autti-Rämö I et al.: Expanding screening for rare metabolic disease in the newborn: an analysis of costs, effect and ethical consequences for decision making in Finland. *Acta Paed* 2005;94:1126-1136.

Diseases evaluated

- congenital adrenal hyperplasia
- MCAD
- LCHAD
- phenylketonuria
- glutaricaciduria

Cost-effectiveness

- The yearly running cost of screening all the 56 000 newborn for the chosen five disorders were estimated to be 2,5 million euros or 45 euros per newborn. The costs per QALY gained (quality adjusted life year) would be from 5 500 to 25 500 euros.

	Ethical aspects when no screening	Benefits of screening	Ethical aspects and possible harms when screening
A newborn, affected with the disease	Risk of death or severe handicap. The risk remains over lifetime	Early diagnosis and treatment gives possibility to remain symptom free.	Commitment to lifelong treatment may cause psychological stress. Identification of a disease form that might not have caused symptoms during lifetime
Newborn with one gene mutation, a carrier	Carrier status unknown which may have either positive or negative consequences for the individual	Knowledge of being a carrier and possibility for genetic counselling	Carrier status identified before being able to give consent for testing
Healthy newborn	No unnecessary examinations	Exclusion of disease	Pain caused by taking the blood sample. Unnecessary examinations when testing falsely positive
Parents of an affected child	Bitterness of parents when the child dies or is severely handicapped from a disease that could have been screened for. Feeling of unfairness when comparing the cost-effectiveness of screening to other implemented treatments.	Possibility to keep the child symptom free with proper treatment. Possibility for genetic counselling.	Identification of a severe disease in a symptom-free newborn. Commitment to lifelong treatment. Stress and fear for life-threatening situations (infections).
Parents of a healthy child	No information on the existence of rare disorders	Exclusion of the disease.	Parents of healthy children unnecessarily disturbed by the offer of screening or worried at false positive screening result
Siblings of an affected child	Knowledge of possibility of being a carrier comes through death or handicap of sibling which may be frightening. Hidden or mild forms not identified.	A possibility to test for being a carrier and get genetic counselling when needed. Identification of a disease that has been symptom-free.	Fear for being a carrier. Identification of disease that might not have caused any symptoms during lifetime.
Close relatives of an affected child	Knowledge of possibility of being a carrier comes through death or handicap of relative, which may be more frightening. Hidden and mild forms not identified and thus the risk of being a carrier is not known	Identification of genetic risk and possibility for genetic counselling.	Fear for being a carrier.
Health care system	Need to evaluate whether diagnostic and treatment possibilities are properly organized. Acceptance of the possibility that some infants may die or be severely handicapped due to delayed diagnosis.	The possibility to prevent permanent damage. Clarification of treatment and follow-up responsibilities from newborn through adulthood	The personnel at outpatient maternity units need to inform parents about disorders they have never encountered. Acceptance of b false positive and false negative results.
Society	Need to evaluate equity in relation to other rare conditions, expensive treatments in use and active screening programmes.	Lower treatment cost for cases. General knowledge about rare conditions increases.	High yearly running costs. Death or handicap of a few at the cost of causing mild side-effects in many. The high cost of treating a handicapped person are unintentionally emphasized.

Consequences to a newborn with one gene mutation, a carrier

If no screening:

Carrier status unknown which may have either positive or negative consequences for the individual

Benefits of screening:

Knowledge of being a carrier and possibility for genetic counselling

Possible harms of screening:

Carrier status identified before being able to give consent for testing

A detected CF "carrier"?

- Incertainty of whether the baby is carrier or affected
- For instance, if the baby is found to have the $\Delta 508$ mutation, an intensive search for an undetected mutation in the other allele and/or a sweat test must be performed.
- The waiting time for additional investigations to be completed is **extremely stressing to the family.**

Potential **benefits** of detecting a carrier: mostly for the family!

- the detection of carrier couples (though difficulty in ruling out carrier couples!)
- presymptomatic testing of these couples' previous children who may have undetected disease
- a carrier parent informing his/her extended family members of the chance of also being a carrier.
- the child will know about the carriership in good time

Potential **harms** of detecting a carrier: mostly for the newborn!

- all problems associated with testing children
 - loss of privacy
 - loss of autonomy
 - stigmatizing the child
 - the difficulty of informing the result to the child correctly and at an optimal time
 - getting knowledge which theoretically may create problems in a future health care system
- **worry and anxiety, especially immediately after the preliminary result**

Carrier testing in children

- We have retrospectively investigated families, where children (now adults) have been tested for carriership of Duchenne muscular dystrophy or Hemophilia A or B.
 - Järvinen O et al: Carrier testing of children for two X-linked diseases: a retrospective study of comprehension of the test result and social and psychological significance of the testing. *Pediatrics* 2000; 106:1460-1465.

Carrier testing in children

- In our study: **About half of the daughters in DMD and Hemofilia families had not been told their test result or recalled them inaccurately.**
- Thus the argument of the usefulness of detecting carriers in newborn screening is even more questionable!

Benefit to the family/harm to the newborn?

- "The complexity and cost of healthcare delivery systems may set up tension between what is good for the society as a whole and what is best for the individual patient."
 - Tavistock group: Shared ethical principles for everybody in healthcare. BMJ 1999;318:248-251.

A clinical geneticist's view

- The problems in newborn screening programs are, in the end, problems of pre-test and post-test information and counseling.
- Optimally, the problems, including detecting carriers, should have been discussed with the couple before the screening test, but, in reality, this is impossible in population screening programs.

A clinical geneticist's view

- The planning, performing and evaluating of (newborn) screening programs should give special emphasis to the availability of comprehensive pre-test information to those who want it and ample resources for immediate support and (genetic) counselling in case of results suggesting to the individual being affected (or a carrier).

