

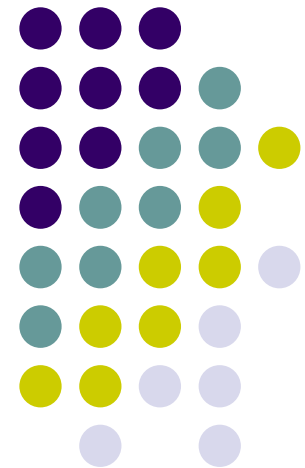
# Are there technical solutions for ethical dilemmas in NBS?

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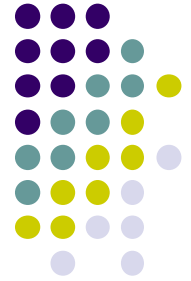
Viktor Kožich

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National Coordination Center for Neonatal  
Screening



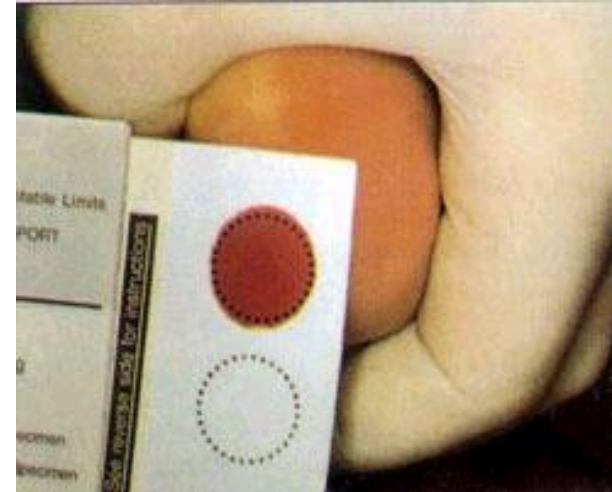
# Outline



- **Introduction NBS**
- Ethical principles in medicine
- Ethical principles in NBS
- Summary

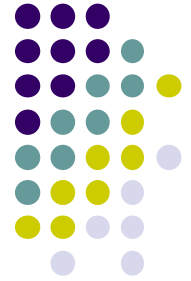
# Neonatal screening

- Search for increased disease risk in presymptomatic newborns
- Complex public health system-not only a laboratory analysis of DBS
- Founder-Prof. Robert Guthrie 1916-1995





JMG Wilson and G Jungner:  
**Principles and Practice of Screening for Disease, WHO 1968**



# Classical criteria for NBS

(Wilson & Jungner)

- Disease frequency and severity
- Asymptomatic latent phase
- Disease mechanisms are known
- Reliable test
- Test is acceptable by the population
- Program is a continuous process
- Acceptable treatment
- Conditions for dx and rx established
- Consensus on whom and how to treat
- Cost-benefit ratio acceptable by the system



# Domains in NBS programs

## Societal values

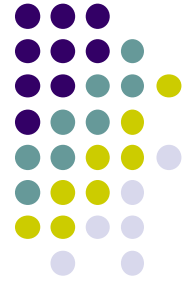
- Health as a value
- Costs (Dx, FU and Rx)
- Societal gains
- Governance

## Information

- Pretest information for parents
- Consent
- Education of HCP
- Counselling

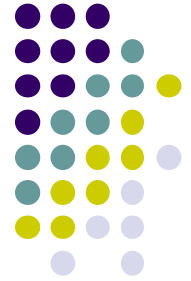
## Samples

- DBS collection
- Lab analyses
- Second tier approaches
- Reporting
- QA
- Secondary use



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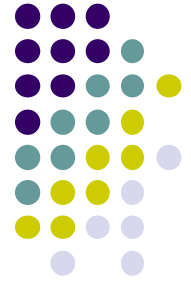


## Ethics (Wiki definition)

...“ Ethics, sometimes known as philosophical ethics, ethical theory, moral theory, and moral philosophy, is a **branch of philosophy** that involves systematizing, defending and recommending **concepts of right and wrong conduct**, often addressing disputes of moral diversity.....



# Wiki-cont'd



....Ethics **seeks to resolve questions** dealing with **human morality**—concepts such as good and evil, right and wrong, virtue and vice, justice and crime....

# Oath of Hippocrates

I swear by Apollo, the Physician, and Aesculapius and health and all-heal and all the Gods and Goddesses that, according to my ability and knowledge, I will keep this oath and

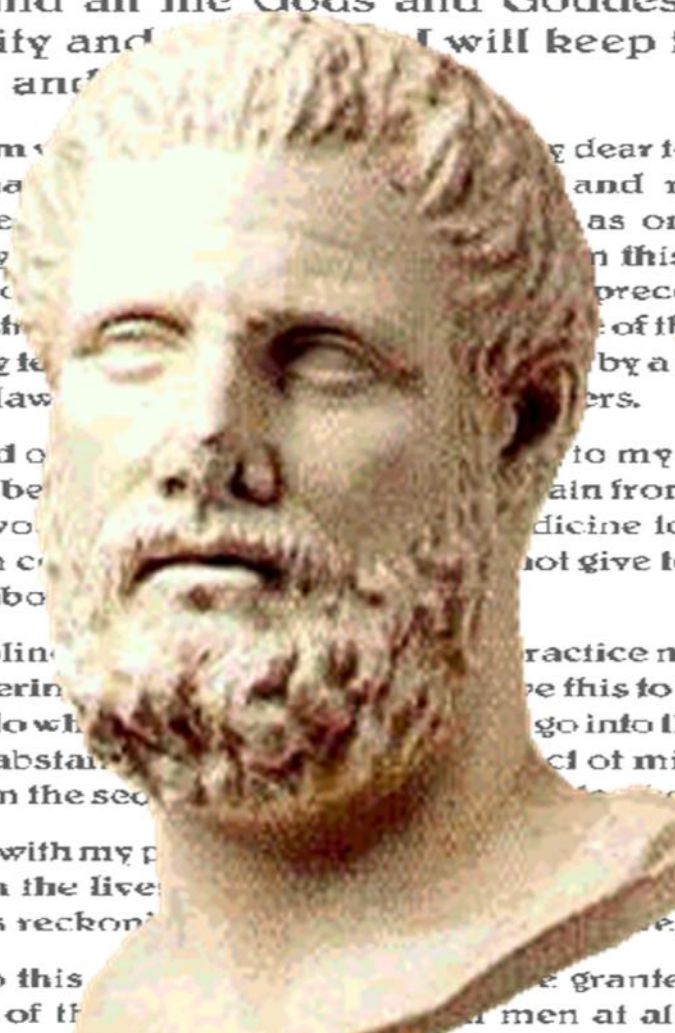
**T**o reckon him dear to me as my parents, to share with him the necessities it requires, and to be on the same footing with my pupils, I will teach them this art if they should wish to learn it, without price, precept, lecture and every other mode of instruction, to my own sons and to those of my family, and to all my disciples by a stipulation and oath, according to the laws of the country.

I will follow that method of instruction to my ability and judgment, I consider for the benefit of the sick, that I will not give pain from whatever cause it may be, I will abstain from whatever is deleterious and mischievous, I will not give to a woman an instrument to produce abortion.

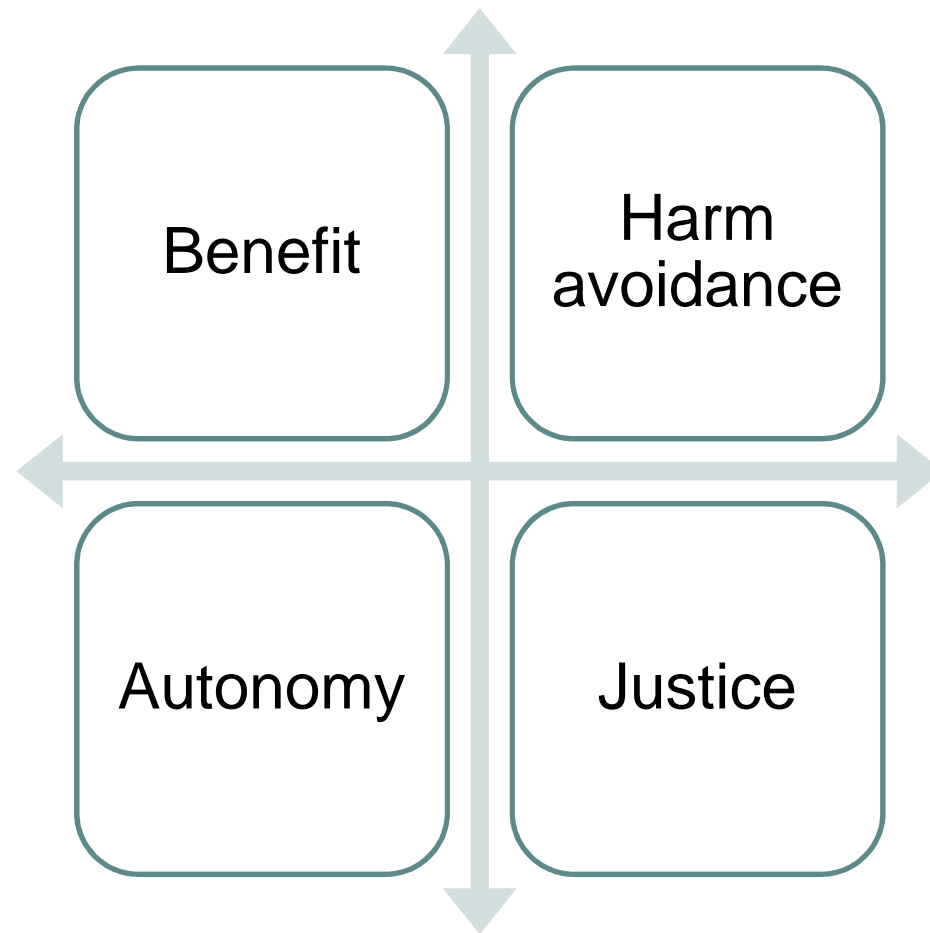
**With Purity** and with Holiness I will practice my art. I will not cut a person who is suffering from a stone, nor will I be this to be done by practitioners of this work. Into the houses of the sick I will go into them for the benefit of the sick and will abstain from every mischief and corruption; and further from the seduction of the sick, and of a woman, and of a slave, and of a free.

**Whatever**, in connection with my practice, I may see or hear in the lives of men, which should not be spoken abroad I will not divulge, as reckoning that all such things should be kept secret.

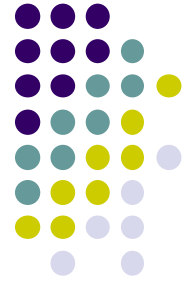
**While** I continue to keep this oath, I will be granted to me to enjoy life and the practice of the art in all its branches, and men at all times but should I trespass and violate this oath, may the reverse be my lot.



# Biomedical ethics-principles



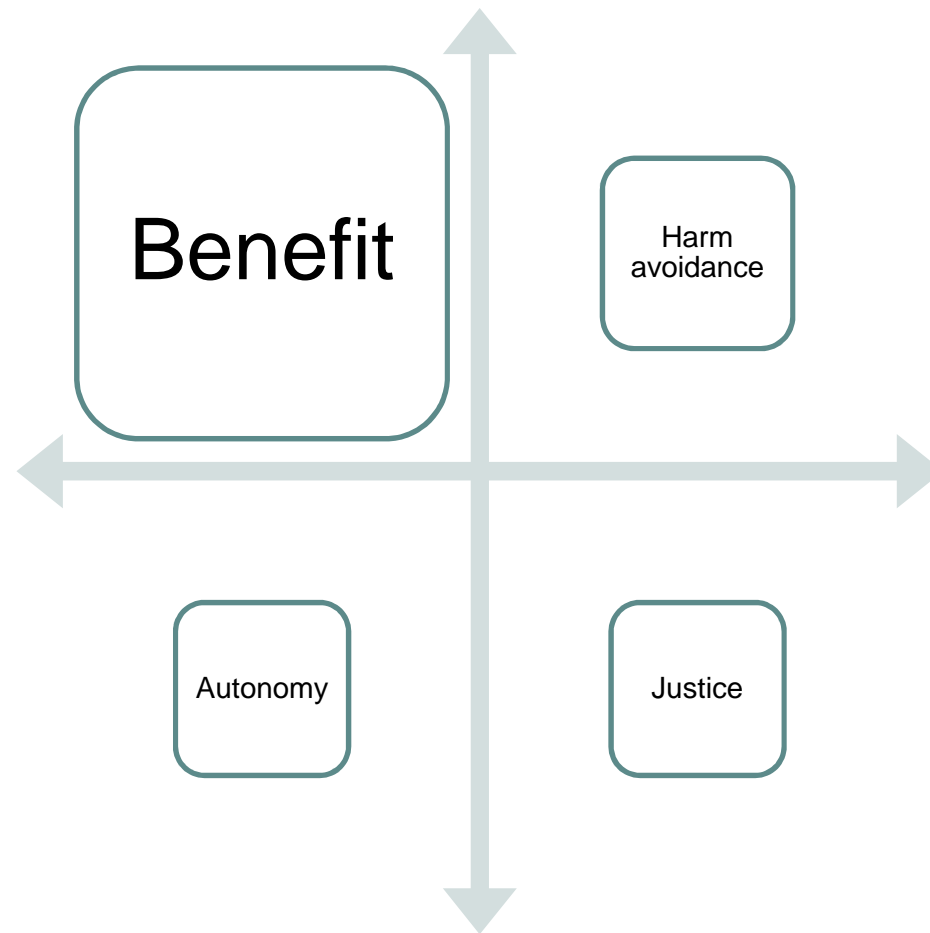
T.L.Beauchamp a J.F.Childress (1979): Principles of Biomedical Ethics



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# Biomedical ethics-principles

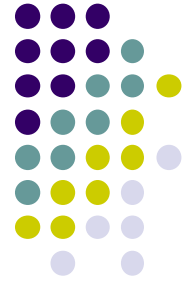


T.L.Beauchamp a J.F.Childress (1979): Principles of Biomedical Ethics

# Assessing benefit in NBS programs



- Natural course of many screened IEMs unknown
  - Ascertainment bias- symptomatic patients (e.g. 3-MCC deficiency)
  - Missed mild cases in NBS (e.g. CBS deficiency)
  - Penetrance of some genetic variants may be incomplete (e.g. MCAD and CBS deficiencies)
- Treatment strategies differ
- Long term follow-up of cases detected by NBS lacking for most IEMs
- Highest level of evidence not available (no RCTs)



# Benefit for patients

- The most important factor
- Which measure of outcome?
  - Early death avoidance?
  - Length of life?
  - Degree of handicap prevented?
  - Overall quality of life?
  - Independence?

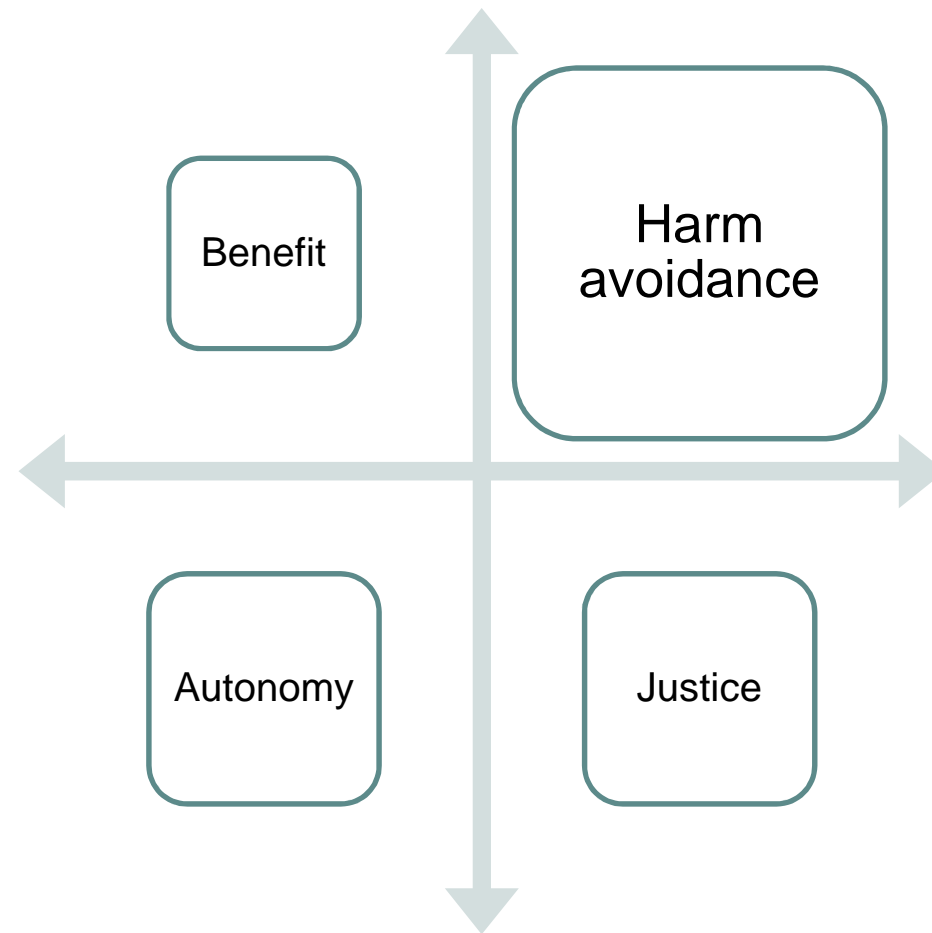
# Benefit for family and society



- Emerging secondary factors
- Considered even for untreatable disorders
- **Benefit of NBS for family**
  - Avoidance of home-care and dependance
  - Reproductive choices
  - Shortening of diagnostic odyssey
- **Benefit for society**
  - Societal wealth produced by patient



# Biomedical ethics-principles



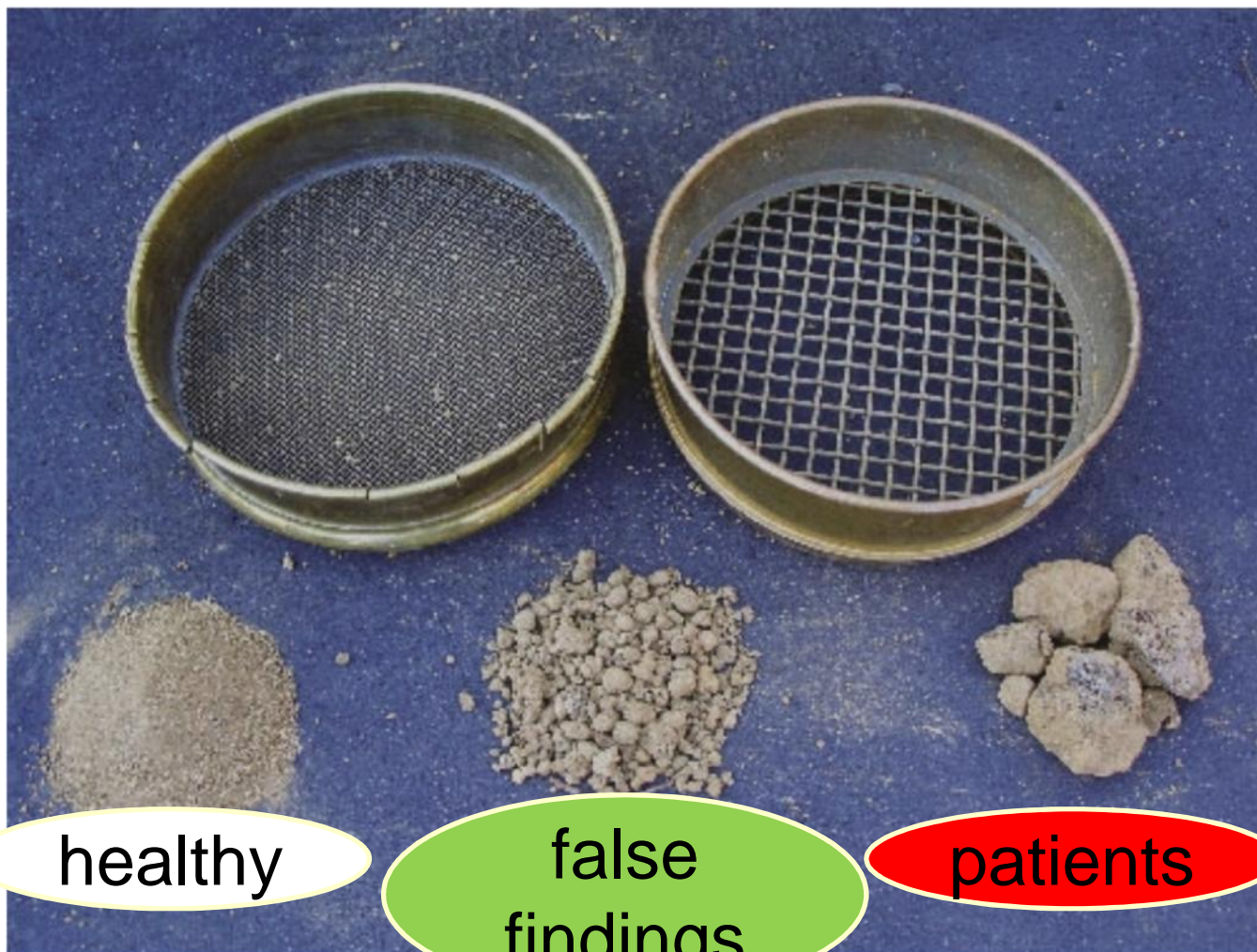
T.L.Beauchamp a J.F.Childress (1979): Principles of Biomedical Ethics



***„All screening programmes do harm. Some do good as well and of these, some do more good than harm at reasonable cost.“***

Sir Muir Gray

former programme director of the National Screening Committee in UK



healthy

false  
findings

patients

# Can NBS elicit harm to the newborn?



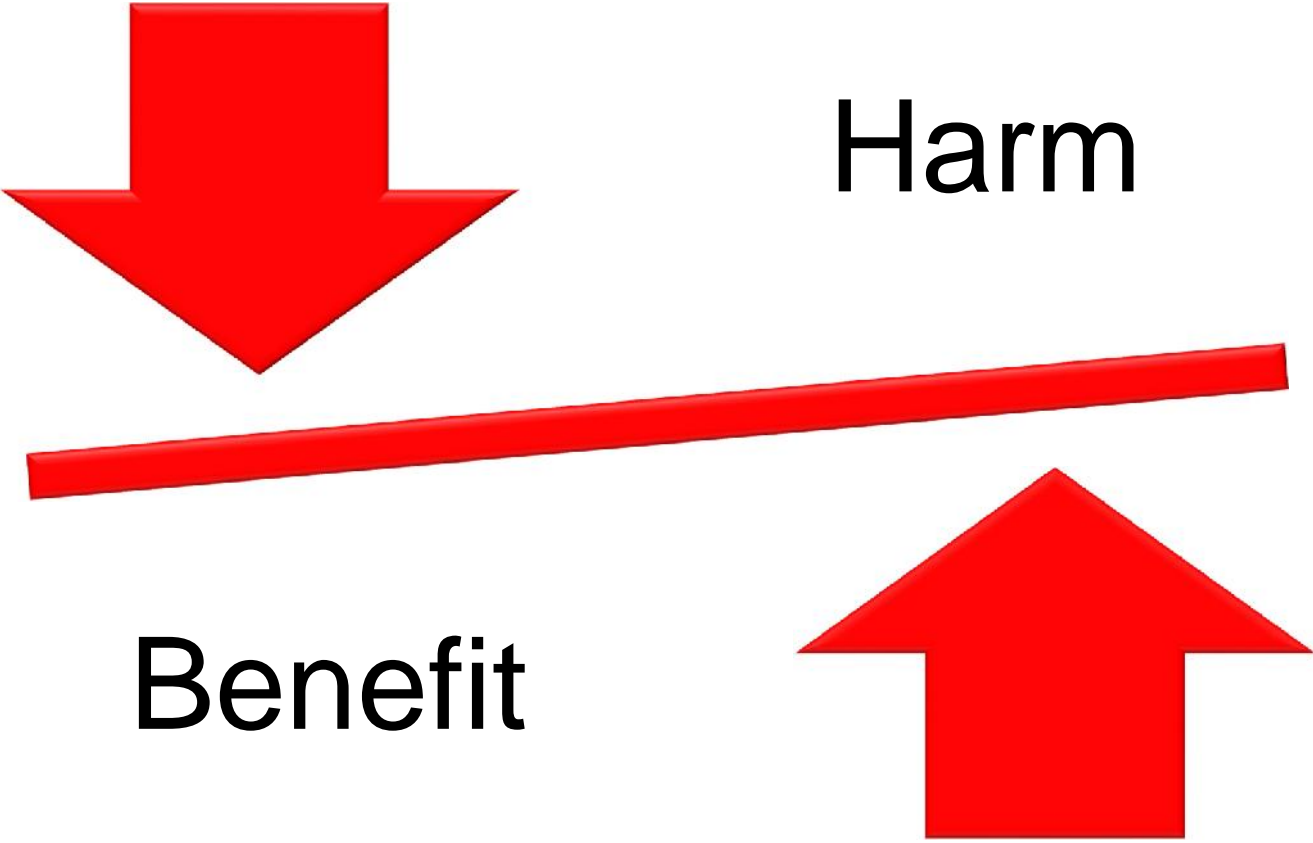
- False positive result
  - Unnecessary further testing
  - Increased long-term medical attention
- True positive result with unknown clinical significance
  - Case definition (e.g. MCAD)
  - Natural history/ascertainment bias (e.g. 3-MCC)
  - Unnecessary therapeutic and/or dietary measures (e.g. MCAD)
- False negative result
  - Missed opportunity to treat (e.g. CBS)
  - Negligence of Dx by HCP

# Can NBS elicit harm to the family and society?

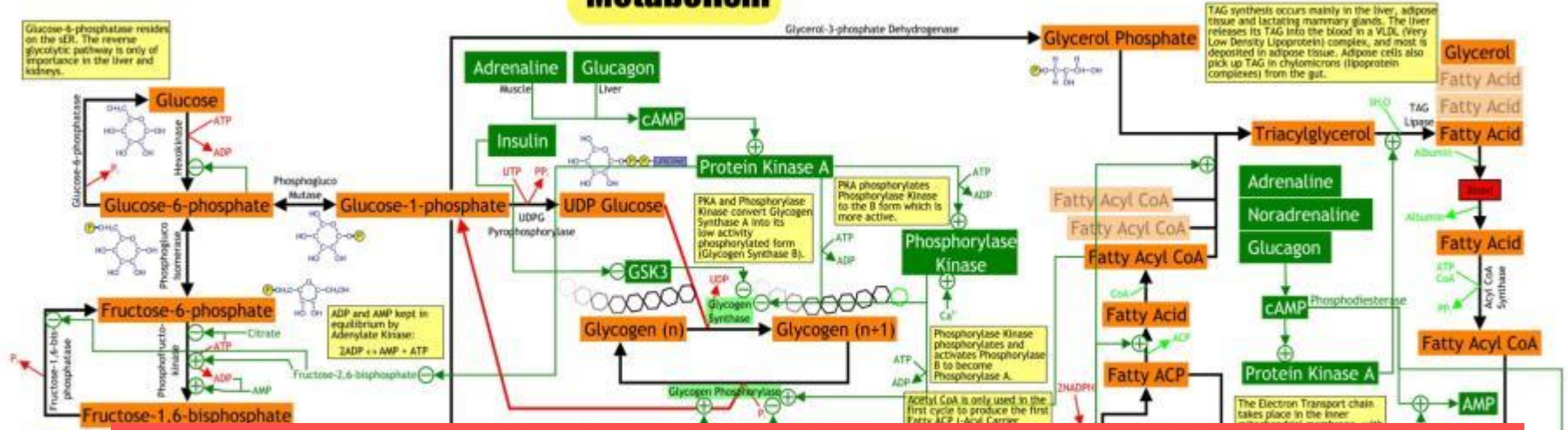


- False positive result
  - Increased stress
  - Impaired child-parent relationship
  - Increased cost to society
- Number of diseases in panel
  - Increased number of false positive cases

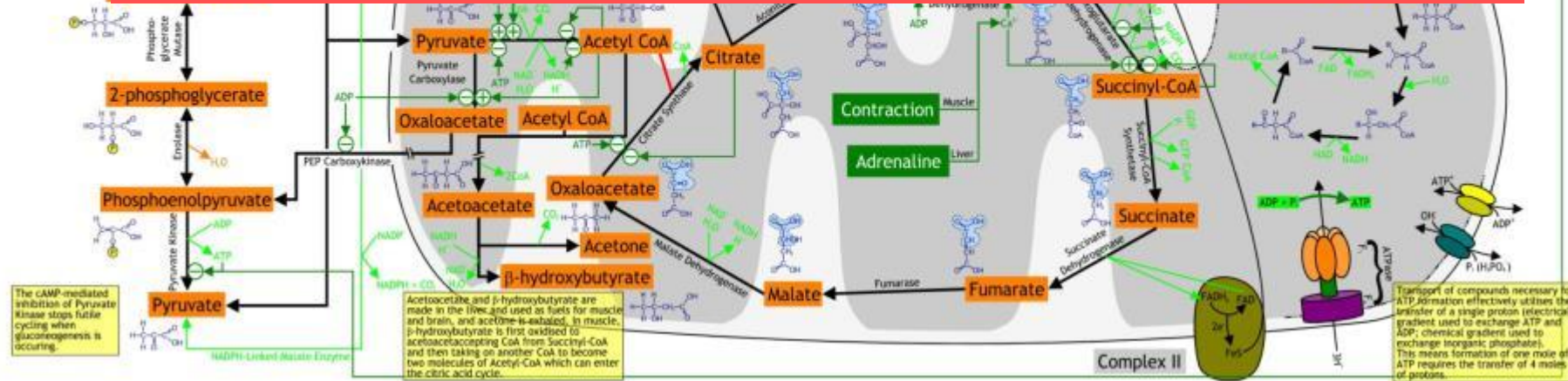
# Dilemma in NBS



# Metabolism



**KEY QUESTION:**  
**WHICH DISORDERS TO SCREEN?**





J Inherit Metab Dis  
DOI 10.1007/s10545-012-9483-0

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SSIEM SYMPOSIUM 2011

## **Newborn screening programmes in Europe; arguments and efforts regarding harmonization. Part 1 - From blood spot to screening result**

**J. Gerard Loeber • Peter Burgard • Martina C. Cornel •  
Tessel Rigter • Stephanie S. Weinreich • Kathrin Rupp •  
Georg F. Hoffmann • Luciano Vittozzi**

Published online: 03 May 2012





# Europe 0-29 diseases

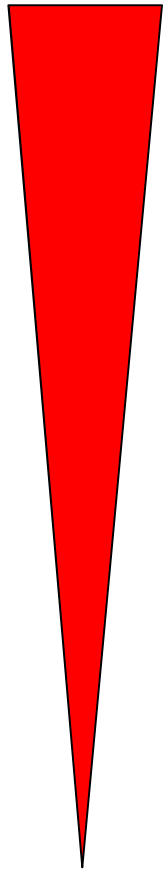
Table 2 (continued)

Country	3hmg (OA)	bkt (OA)	mma (OA)	mcadd (FAOD)	vlcadd (FAOD)	lchadd (FAOD)	cptI (FAOD)	cptII (FAOD)	cud (FAOD)	scadd (FAOD)	schadd (FAOD)	decr (FAOD)	s-s (Hemo)	btha (Hemo)	sc (Hemo)	bio (M)	galt (M)	udp (M)	N disorders screened for
Albania																			0
Austria		X		X	X	X	X	X	X	X						X	X	X	29
Belgium (Flemish)				X												X			11
Belgium (French)																	X		8
Bosnia-Herzegovina																			3
Bulgaria																			3
Croatia																			2
Cyprus																			2
Czech Republic				X	X	X	X	X											12
Denmark				X	X	X			X							X			15
Estonia																			2
Finland																			1
France													X						5
FYROM																			1
Germany				X	X	X	X	X								X	X	X	15
Greece																	X		3
Hungary	X	X		X	X	X	X	X	X	X						X	X		25
Iceland	X	X	X	X	X	X	X	X	X	X	X								26
Ireland																	X		5
Italy																			3
Kosovo																			0
Latvia																			2
Lithuania																			2
Luxembourg				X															4
Malta														X	X				3
Montenegro																			1
Netherlands	X			X	X	X							X	X	X	X	X		20
Norway																			2
Poland																			3
Portugal	X			X	X	X	X	X	X		X								25
Romania																			2
Serbia																			2
Slovakia																			4
Slovenia																			2
Spain	X			X	X		X	X	X				X			X	X		27
Sweden																X	X		5
Switzerland <sup>1</sup>				X												X	X	X	7
Turkey																X			3
United Kingdom				X									X	X	X				7
Frequency	5	3	1	13	9	8	7	7	6	3	2	0	4	3	3	10	10	3	

<sup>1</sup> including Liechtenstein

<sup>2</sup> Belgium (French) screens for CAH not nationwide; likewise Italy screens for CF but not nationwide

# Types of diseases in screening programs



1. Disorders for which **considerable, irreparable damage can be prevented** (e.g. PKU, CH, MCADD)- at least for their typical forms.
2. Diseases for which screening and early care **prevent acute morbidity but do not change the long-term complications** (e.g. galactosemia)
3. Disorders for which there is less substantial or **insufficient evidence of damage prevention** (many organic acid, amino acid, or fatty acid metabolic diseases)
4. Disorders for which **damage to health cannot be prevented** (e.g. Duchenne muscular dystrophy)

# Technical solutions in NBS- benefit vs. harm



## Disease knowledge

At Dx registries

FU registries

Research

## Tests development

Second tier

Postanalytical

New techniques

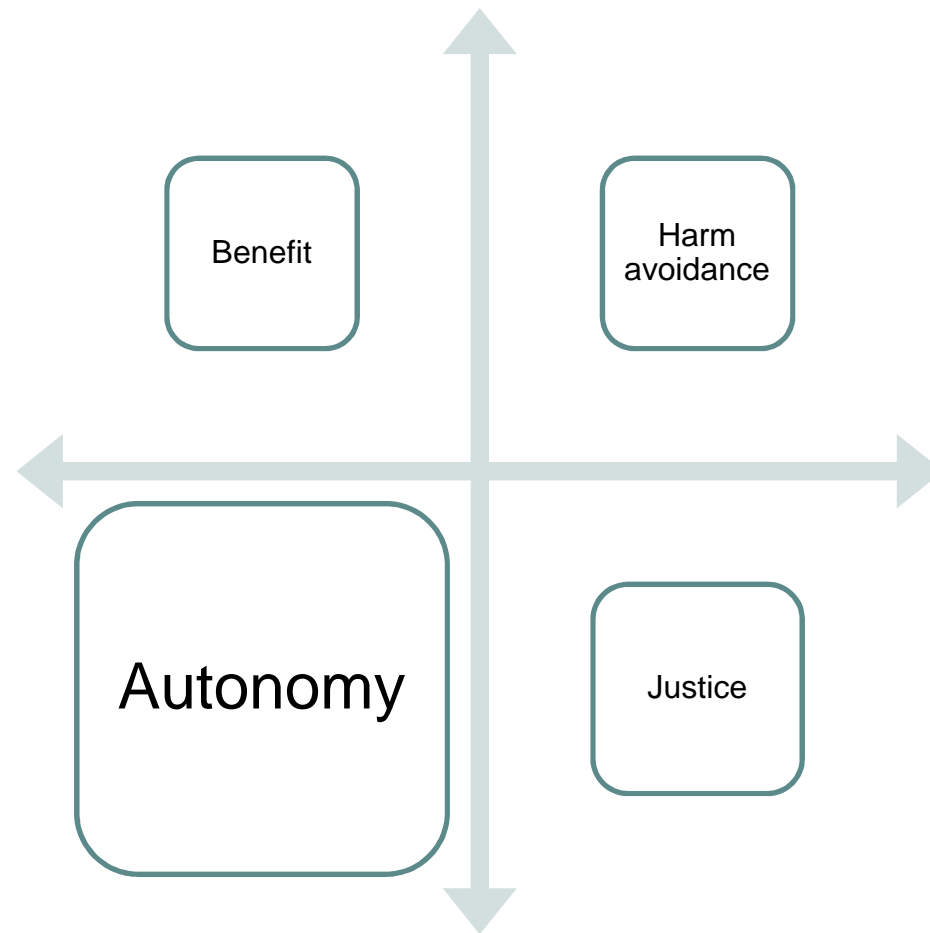
New markers

## Treatment

Evaluation of  
existing Rx

Development of  
new Rx

# Biomedical ethics-principles



T.L.Beauchamp a J.F.Childress (1979): Principles of Biomedical Ethics

# Autonomy in NBS programs



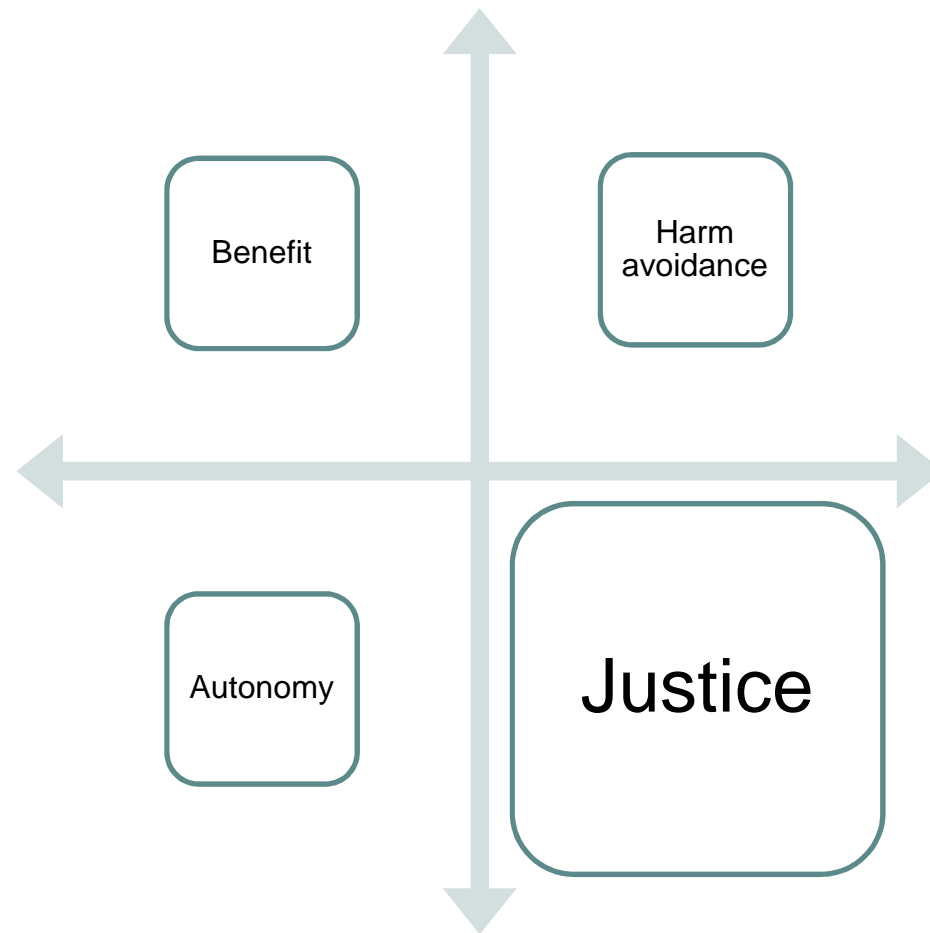
- „...newborn screening should be mandatory and free of charge if early diagnosis and treatment will benefit the newborn“... WHO, 2000
- Can parents refuse NBS?
- Is information for parents sufficient to make informed decision?
- What should be the information content?
- Informed consent requested? Opt-out or Opt-in approach?

# Autonomy and DBS storage

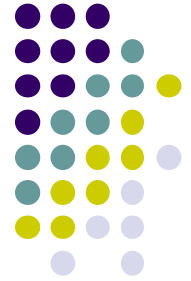


- Storage varies widely: 3 Mo (D) to indefinite (DK), median in EU 8 years
- Reasons for storage
  - FP and FN analysis
  - Research/marker development
  - Forensic use
- Newborn did not consent to storage
- Parents may not be aware of storage
- Movements to destroy DBS (human right activists) and to preserve DBS (RD-POs)

# Biomedical ethics-principles



T.L.Beauchamp a J.F.Childress (1979): Principles of Biomedical Ethics

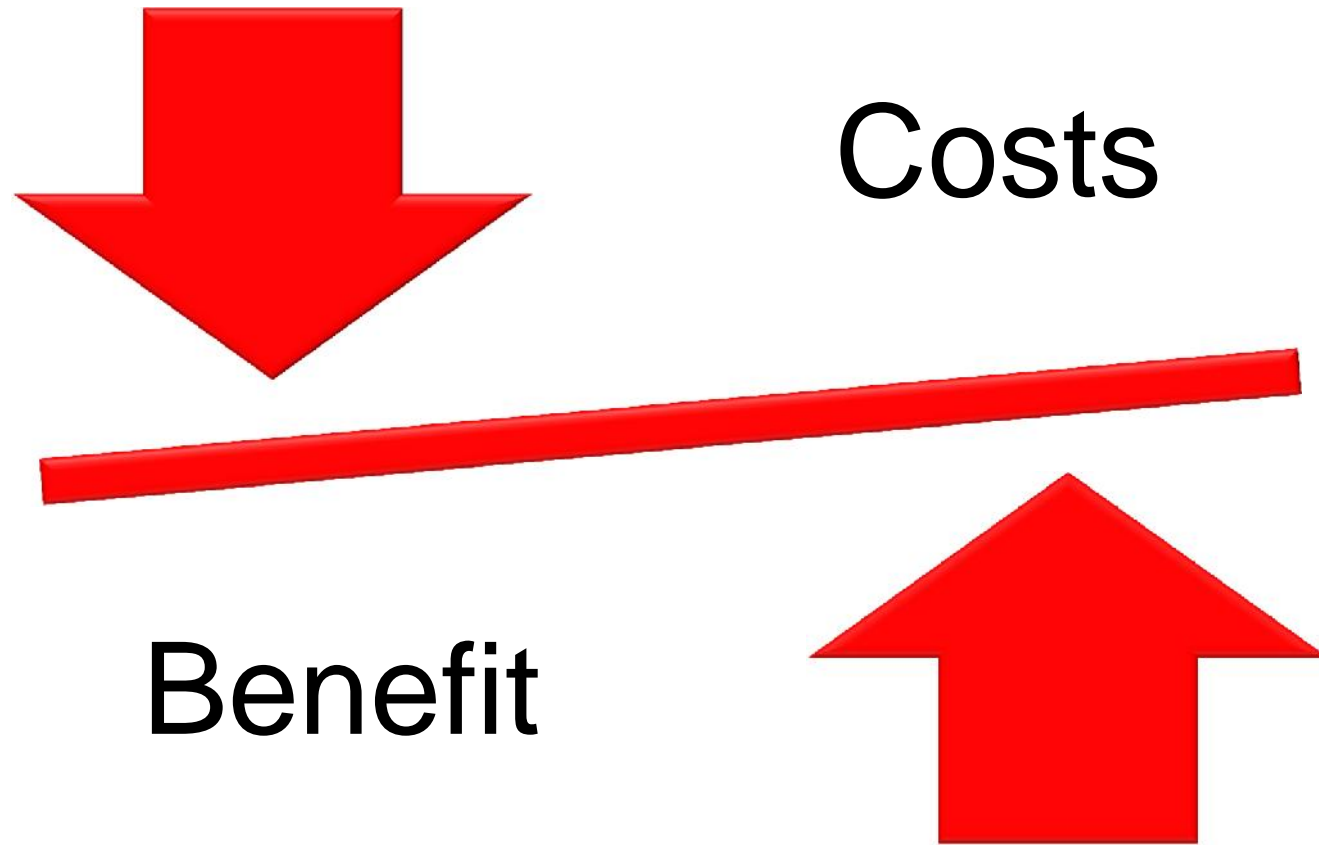
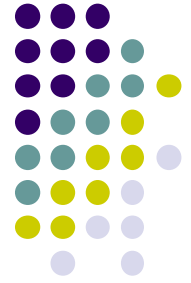


# Justice and NBS

- Justice in distribution of limited resources within the health care system
- Balancing different programs based on costs and proportion of patients in society
- Cost effectiveness analyses (including QALYs and willingness to pay) as decision tools
- Value driven decisions for RDs („castaway rescue“)



# Dilemma in NBS





# Newborn Screening in Europe What can be expected ?

ISNS 2011

Geneva, 28 August 2011

[segolene.ayme@inserm.fr](mailto:segolene.ayme@inserm.fr)

Paris, France

orphanet

[www.orpha.net](http://www.orpha.net)

# Conflicts of interest obscure the debate

- Expert biologists have a strong research interest in developing their discipline
- Manufacturers of robots have a strong interest in the translation of research results into practice: nothing better than a population approach
- Politicians have a strong interest as screening is popular in public opinions
- Patients organisations have a strong interest as they anticipate to benefit from a focus on their disease even if NBS is not fully justified

WHO is strong enough to counterbalance ?

# Technical aids in NBS- autonomy and justice



## Information

Pre-test info

Governance

Consent

Storage time

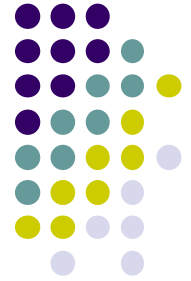
## Cost benefit

HTA tools

Orphan drugs

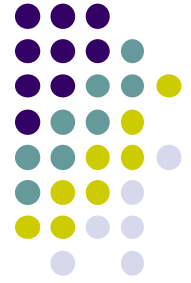
Lab tests

**Final decisions are political**



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# Conclusion

- NBS programs associated with a number of ethical issues
- Technical solutions may resolve some benefit/harm problems
- Autonomy and justice issues are more value-related and depending on political decisions
- Adequate attention should be given to ELSI in developing and evaluating NBS programs

# Acknowledgement

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- P.Ješina



