Recommendations to the ACHDNC for Newborn Screening of Mucopolysaccharidosis Type II (MPS II)

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ACHDNC Meeting

February 10, 2022

Decision Matrix

- Understanding the level of certainty of net benefits of newborn screening for identification of infants affected by MPSII in the population*
- Feasibility of newborn screening for MPSII
- States' readiness to implement newborn screening for MPSII

Decision Matrix for Nominated Conditions for the Recommended Uniform Screening Panel (RUSP)

NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.			---	
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.			---	
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.			---	
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Mucopolysaccharidosis type II

Characterization and epidemiology

- X-linked lysosomal storage disorder
- Variants in the *IDS* gene lead to dysfunction in the enzyme, iduronate-2-sulfatase (I2S) with the accumulation of glycosaminoglycans (GAGs), dermatan sulphate and heparan sulphate, in organs
- Prevalence: Japan and Taiwan reported (0.84-1.07 per 100,000 births); in the U.S. estimated (0.26 per 100,000)
- Based on newborn screening estimates (MO and IL) 1.2-1.6/100,000
- Affects primarily males with occasional identification of symptomatic females

Mucopolysaccharidosis type II

Screening and Diagnosis

- **Screening** by enzyme analysis: two methods reported for detection after incubating substrate with the DBS
  - Fluorometric
  - MS/MS
  - 2nd tier examination of DBS GAGs can reduce the call outs for pseudodeficiency (may be a send out from the NBS labs)
- **Confirming diagnosis**
  - Repeat enzyme assay
  - Measurement of another sulfatase to rule out multiple sulfatase deficiency
  - Genetics:
    - Hemizygous pathogenic variant or deletion in the *IDS* gene; less useful in predicting clinical course
  - Biochemical profile: urinary glycosaminoglycan (GAGs) detection
  - Family history; Carrier detection through siblings or affected persons

Mucopolysaccharidosis type II

Findings and symptoms

- Classification for cases is severe or attenuated
  - Severe – early childhood onset with neurological deterioration;
  - Attenuated – later onset and slower progression, but all patients appear to have some degree of neurological involvement, but adults have normal cognition
- Symptom onset by 2.7 years for severe phenotype; 4.3 years for attenuated phenotype
- Symptoms can include hearing loss, progressive change in appearance, enlarged liver/ spleen, joint stiffness/mobility issues, abdominal hernia, enlarged tongue/tonsils/adenoids, cardiac valve disease, developmental and fine motor issues, behavior concerns
- Presentation and progression of symptoms can be variable

Treatment

- Weekly enzyme replacement therapy, idursulfase (Elaprase®) FDA approved 2006
  - IV over several hours
  - Many develop antibodies, many have reactions that are manageable
- Symptomatic treatment and therapies
- Investigational therapies
  - Hematopoietic stem cell transplantation (HSCT)
  - CNS delivery of ERT
  - Investigational ERT proposed to penetrate the CNS
  - Insufficient evidence is available regarding potential benefit of gene therapy
- ACMG published MPS II guidelines in 2020

Mucopolysaccharidosis type II

Net Benefit/Certainty

- ERT therapy appears to be associated with
  - Moderate delay in mortality
  - Reduced rate of deterioration in mobility, respiratory status, cardiac status
- CNS disease is not directly impacted by existing therapies, but somatic improvements may allow better acquisition of developmental milestones
- Limited evidence supporting benefit of early vs. symptomatic treatment
  - Several sibling pairs reported suggest benefit
  - Complicated by commonly delayed clinical diagnosis
- The peer reviewed evidence base is limited; much of the assessment of value relies on expert opinion
  - This is primarily a result of the ultra-rare nature of the condition

Annual Projected Outcomes for Newborn Screening for MPS II in the U.S.

- Data are projected estimates for annual population-based results based on data from two existing state screening programs.
- ~1 in 8 infants with a positive screen will be diagnosed with some form of MPS II
- ~1 in 8 infants with a positive screen will be followed for some period of time without a definitive diagnosis (1 to 2 years?)
- ~1 in 12 infants with a positive screen will be lost to follow up before a definitive diagnosis can be made

	Newborn Screening
Positive screen	480 (346 - 523)
MPS II identified	59 (**44 - 61**)
Diagnostic uncertainty requiring follow-up	59 (**34 - 218**)
False positive	322 (131 – 352)
Lost to follow-up	41 (34 -87)

Benefit to affected infants/children

- Somatic improvement
- Slower somatic progression
- Possibly slower neurologic degeneration
- Improvement of cardiac and other symptoms
- Improved respiratory outcomes at age 16 years
- Overall survival – median age of death increased by 3.5 years in UK study with ERT
  - Some evidence suggests this difference will increase with earlier treatment

Benefit to affected infants/children

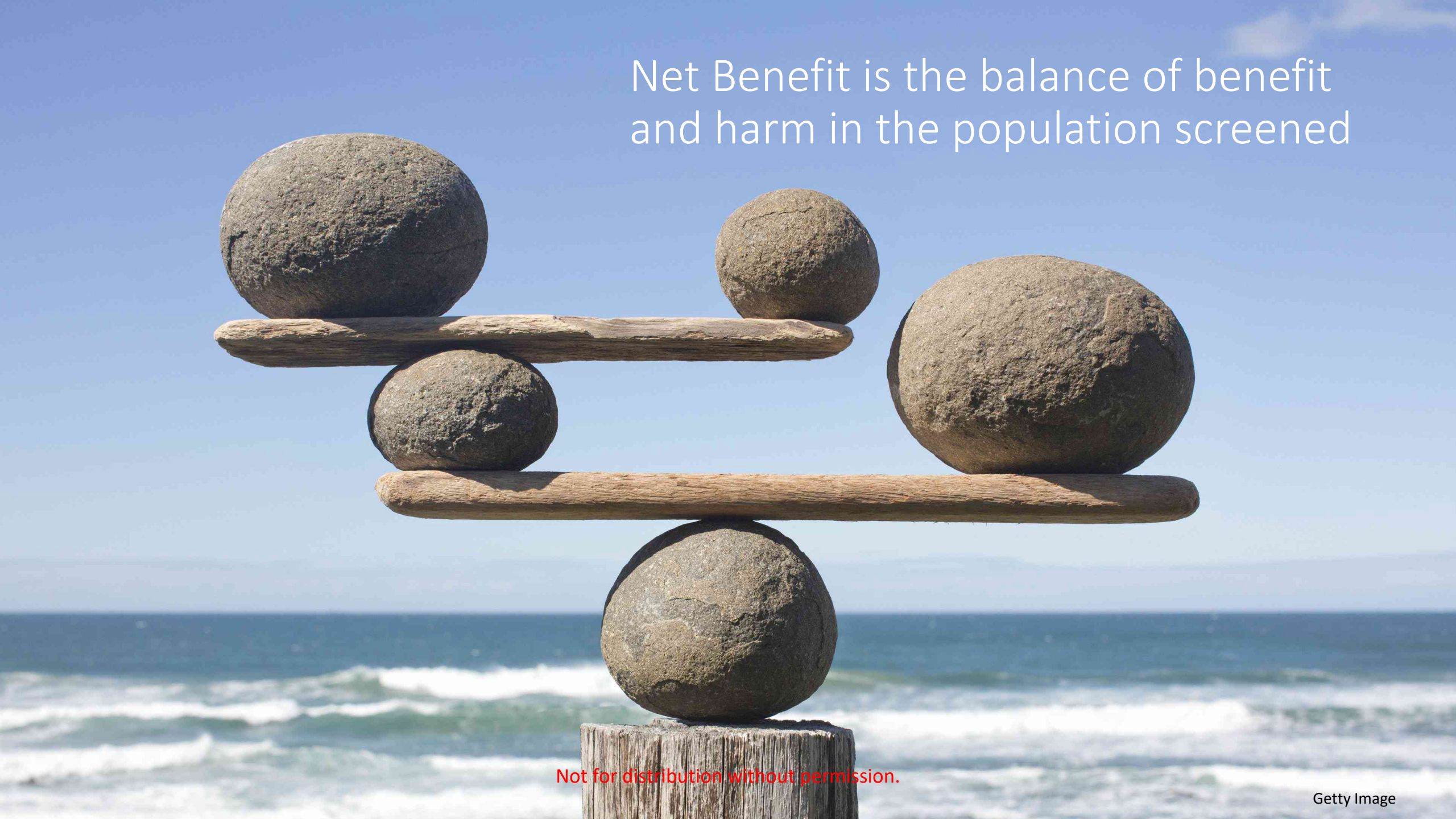
Reasonable assertions based on challenging data

- ERT likely associated with modestly prolonged life
- ERT likely associated with better somatic function, and assume improved QOL
- ERT does not alter CNS outcome
  - Although it has been suggested there may be slowing of rate of deterioration
- Earlier initiation of ERT likely maximizes benefit of therapy
  - Data lacking regarding pre-symptomatic therapy

Potential Harms

- Potential harms of the NBS process primarily due to false positive include
  - VUS and indeterminate results
  - Lost to follow up
  - Pseudodeficiency results
- False negative – none reported yet
- Potential for psychological and financial burdens for families after false positive screen, particularly for indeterminate results
  - Travel to appointments, unrecovered income, time lost
  - Costs of monitoring
  - Quality of life – anxiety and stress for parents

Net Benefit is the balance of benefit and harm in the population screened



Getty Image

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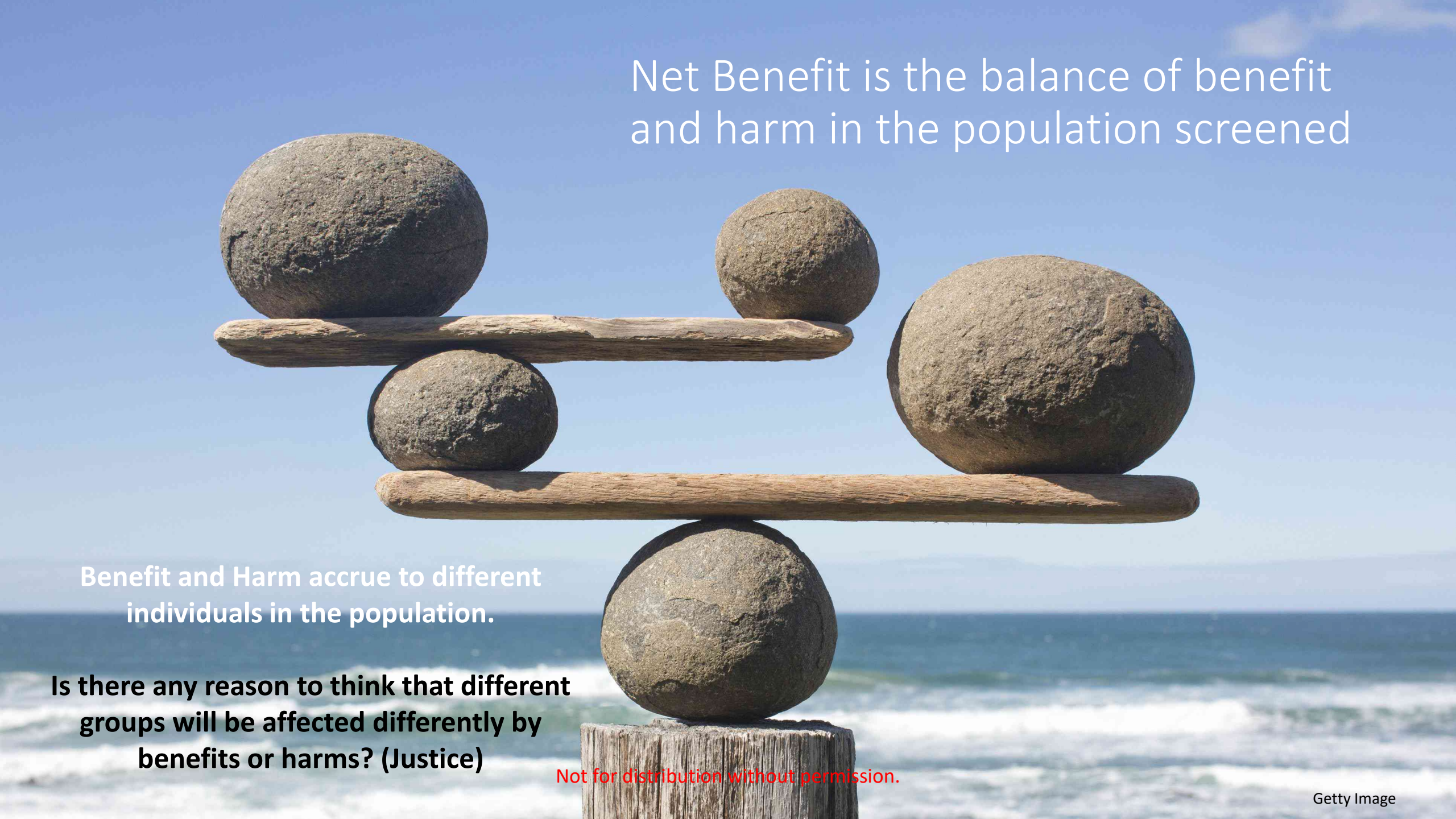

Benefit and Harm accrue to different individuals in the population.

Is there any reason to think that different groups will be affected differently by benefits or harms? (Justice)

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Is there significant net benefit for compulsory, population NBS?

- Moderate, but clearly important to the families, impact of treatment on individual outcome
- Early treatment more likely than not to be better than waiting for symptoms for individuals
- Potential harm to families with indeterminate status
  - Extremely low risk of treating patients that will not benefit from treatment
- Relatively high screening cost per true positive (currently)

High Certainty of **significant** benefit in somatic findings (A)

OR

Moderate Certainty of **significant** benefit in somatic findings (B)

OR

High Certainty of **small** benefit overall - somatic, neurologic, survival (C)

OR

High Certainty of **moderate benefit** in somatic findings (not an option)

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Newborn screening for MPSII

Feasibility and Readiness

- Newborn screening tests are available and appropriate for high-throughput testing
- Proportion of patients awaiting final diagnosis less than ideal
- Proportion of true positive to all positive NBS results is in the range of other conditions on the RUSP
  - Second tier testing highly recommended/required
- Most states could add screening in a reasonable period (1-3 years)
- Marginal screening cost is higher than for some recent additions
- Follow up resources thought to be adequate to demand

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- Newborn Screening for MPSII meets criteria for matrix category B2
- Developmental readiness for newborn screening programs to enact screening for MPSII
- There is High or Moderate evidence of feasibility of screening, testing and treatment in States' newborn screening systems

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