Moving Neonatology into the Modern Era of Drug Development: Overview of Potential consortium projects and deliverables

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Moving Neonatology into the Modern Era of Drug Development: a clinical perspective

Mark Turner

International Neonatal Consortium

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Declarations of interest

Chair, European Network for Paediatric Research at the European Medicines Agency

Publically-funded

- European Commission FP7, NIHR, BLISS, MRC, AMR
- Associate Director (International Liaison) National Institute for Health Research, Children's Theme
- Scientific Coordinator Global Research in Paediatrics (GRiP)

Commercial: Pecuniary, non-personal

- Consultancies
  - Product-specific / National PI: Chiesi, Shire,
  - Non-product-specific: Janssen

A clinician's view of the future

- Vision
- Differences from the present
- Implications for practice

Clinical Vision

Improved outcomes due to new medicines that come to market rapidly

This happens because of:

- Intelligent pipelines for drug development
  - Smart trials
  - Optimise use of existing data
  - Minimise the impact on babies and families
- Feasible studies
- High quality data
  - Line listings, source data verification (SDV)
  - Networks

Different approach to most academic neonatal research

Regulatory studies canNOT rely on

- Cochrane Reviews
- Pragmatic trials

May need to recognise need for different approaches for different purposes
HTA etc.

Examples of differences

- Need for well-qualified standard of care
- Justifiable doses
- Extrapolation
- RCTs may not be the gold standard
  - "Evidence-Based Medicine" needs to be updated

Differences between regulatory and clinical logic

Clinical Logic

- Is it worth trying this medicine in this baby?
  - At this time
  - When I can see what happens next
  - Pharmacy can prepare the medicine for me

SPECIFIC

Regulatory Logic

- Am I able to allow a company to claim that this medicine has a useful effect
  - when given for a specific indication
  - without excessive harm
  - and that it is provided in a form that manufactured to high standards and is appropriate for this age-group

GENERAL

Differences between regulatory and clinical logic

Clinical Logic

- I am responsible for what happens now
- Parents and nurses want me to do something
- I can explain what I'm doing
- I have no influence over the data

Regulatory Logic

- I am responsible for the lifetime of the Marketing Authorisation
- Poor data and poor reasoning has led to therapeutic catastrophes in the past
- Good intentions are no guarantee of a good outcome
- I have legal leverage over the data

Differences between regulatory and clinical logic

Clinical Logic

- Do a trial that helps us make a specific clinical decision
- Take a pragmatic approach to trial design and data collection

Regulatory Logic

- Negotiate with Sponsors to develop a rational pathway to a medicine that, for a specific indication, is of high pharmaceutical quality
- Optimise study conduct with a stepwise approach that uses proxy markers and existing information to narrow the options
- Rigorous approach to trial design and data collection

The impact of clinical logic

"Can the clinician, with the data available from six large-scale clinical trials, make an evidence-based decision about the use of inhaled nitric oxide in premature infants to improve their survival without bronchopulmonary dysplasia? The answer for now seems to be no. Although inhaled nitric oxide might be promising in specific subgroups of infants, more work is needed to define the optimum dose and duration, and the target population in terms of maturity, severity of illness, race, and age at enrolment at which the infant would potentially be most responsive to intervention with inhaled nitric oxide"

NO for preterm infants at risk of bronchopulmonary dysplasia
Sosenko & Bancalari 2010, Lancet 376:308

The impact of clinical logic

- “Medical and surgical interventions are widely used to close a persistently patent ductus arteriosus in preterm infants. Objective evidence to support these practices is lacking…. Emerging evidence suggests that treatments that close the patent ductus may be detrimental…. Neither individual trials, pooled data from groups of randomized-controlled trials, nor critical examination of the immediate consequences of treatment provide evidence that medical or surgical closure of the ductus is beneficial in preterm infants”

Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis?
WE Benitz Journal of Perinatology (2010) 30, 241–252;

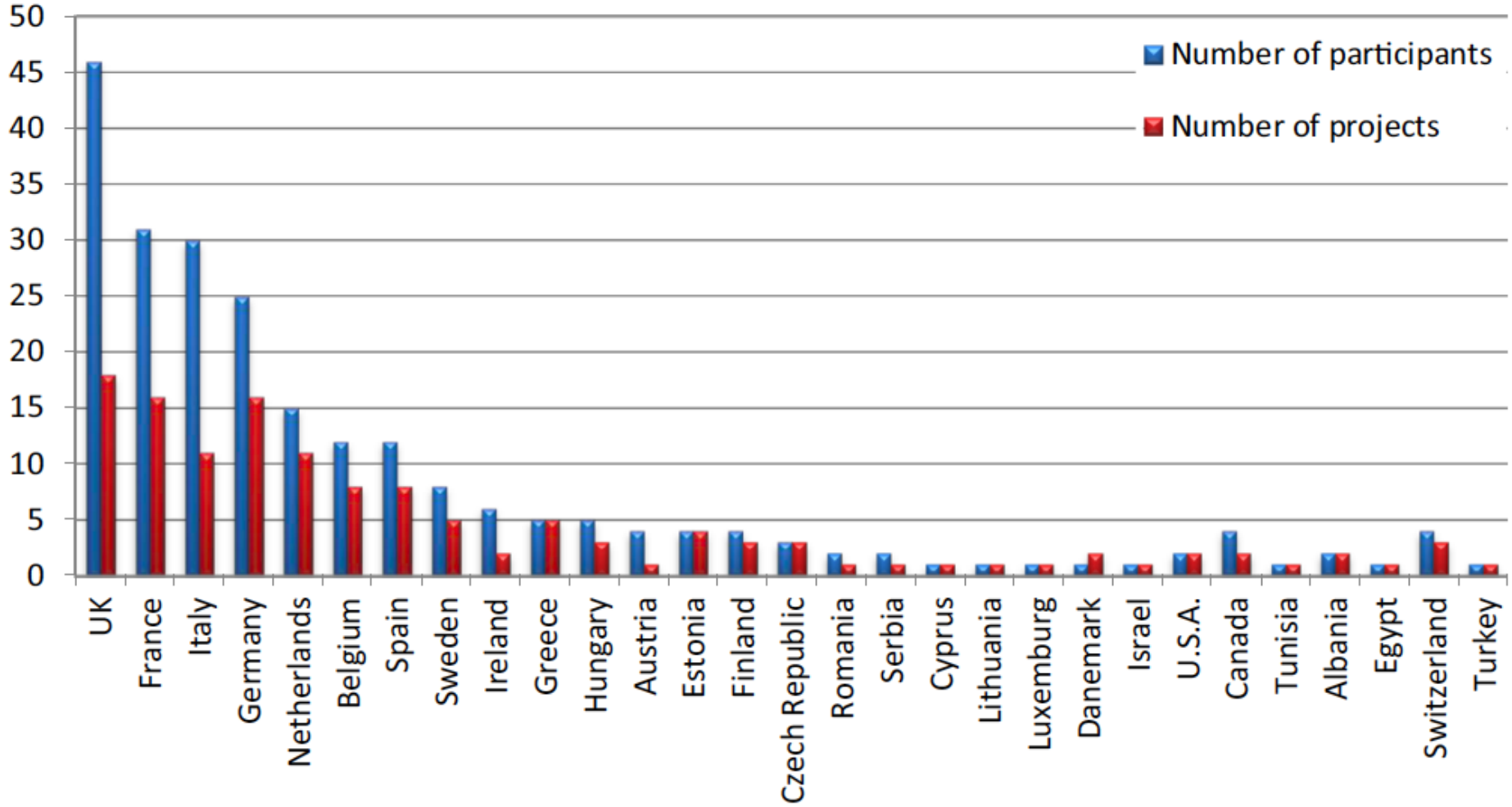
Implications

- Focus on standard of care as much as clinical need because we can't do regulatory standard studies unless the standard of care is well-defined and implemented.
- Do the survey
- Agree standards of care
  - None of us can be sure that we are doing the right thing, why let our prejudices stop research.
- Validate biomarkers
  - as well as think physiologically
- Get the dose right
- Then study efficacy
- Then study the real-world
  - e.g. post-marketing surveillance

Networks

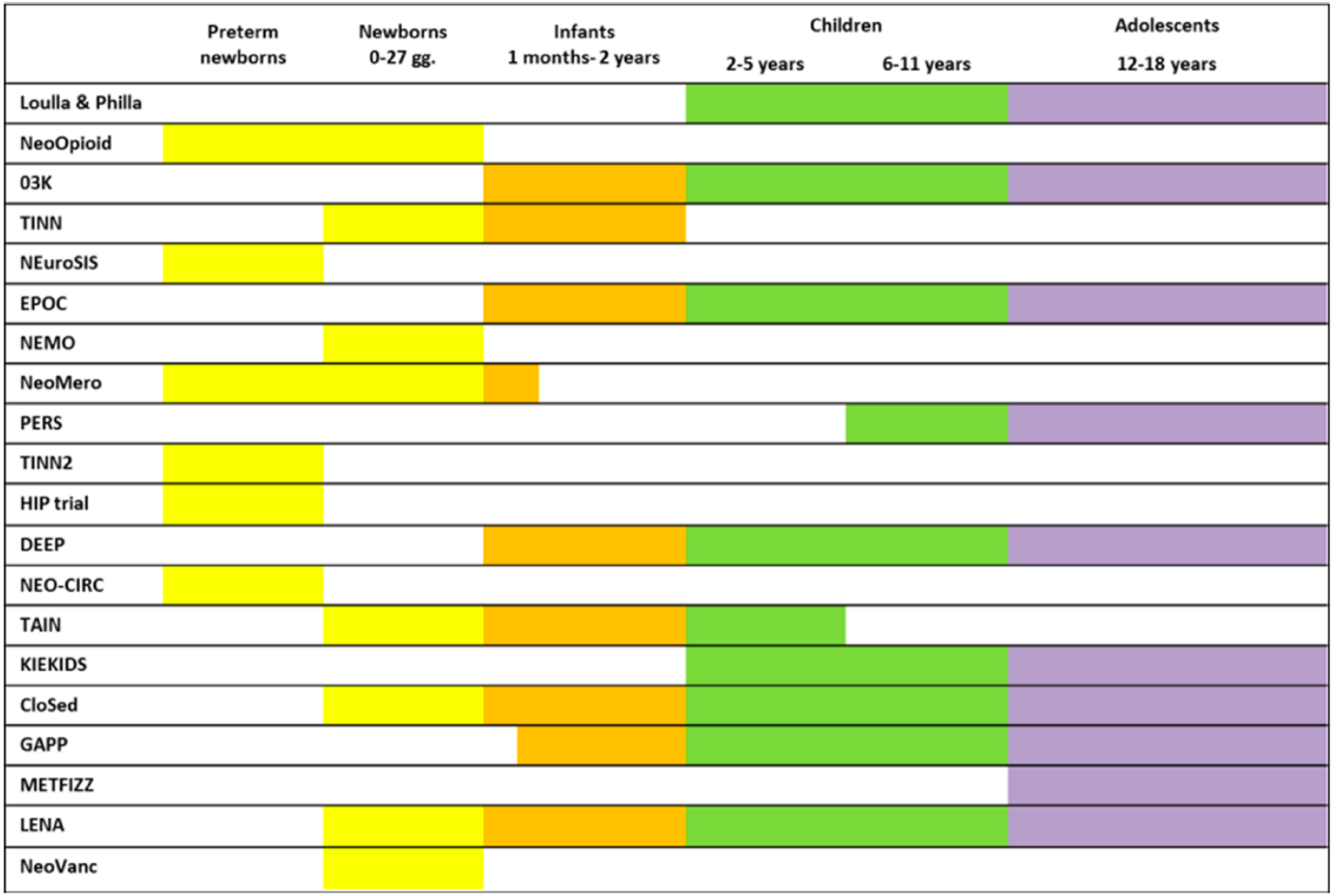
- Reusable infrastructure
- Common standards
- Performance management
- FP7 PUMA projects and PTN show interest in this type of work but a step change in performance is needed

Networks



Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines
Ruggieri et al. Eur J Pediatr. (2015)174:481-91.

Networks



Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines
Ruggieri et al. Eur J Pediatr. (2015)174:481-91.

There is significant enthusiasm for medicines research in Europe

Single point of contact for European networks

enprema@ema.europa.eu

Searchable database

http://enprema.ema.europa.eu/enprema/

Summary

We need:

- Improved outcomes due to new medicines that come to market rapidly
- To move from clinical logic to regulatory logic
- To work in networks

- To develop a shared understanding of regulatory science

Moving Neonatology into the Modern Era of Drug Development: Overview of potential consortium projects and deliverables

Neonatal Drug Development: Industry Perspective

Ronald Portman and Christina Bucci-Rechtweg
Pediatric Therapeutic Area
Novartis Pharmaceuticals

International Neonatal Consortium

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What are the goals of pediatric drug development programs?

- Determine safety and efficacy of the product for the claimed indications in all relevant pediatric populations (same or different than adults): based on need?
- Provide information to support dosing and administration for each pediatric subpopulation for which the product is safe and effective
- Propose labeling
- Use age appropriate and acceptable formulation(s)
- Ensure involvement of child and parent in design and study feedback

Focus on Innovation Management in R&D has Facilitated Pediatric Product Development

R&D

Developing novel outcomes evidence early in process

Portfolio

Enhancing focus on differentiated medicines most likely to **address unmet medical needs; genetic basis for disease**

MDx

Personalizing our medicines:
Driving better patient outcomes through focused solutions and interventions evaluated through innovative trial designs

M&S Tech

Developing innovative technology, study designs, medication delivery, diagnostics, modeling and simulation techniques in R&D to address the needs of special populations

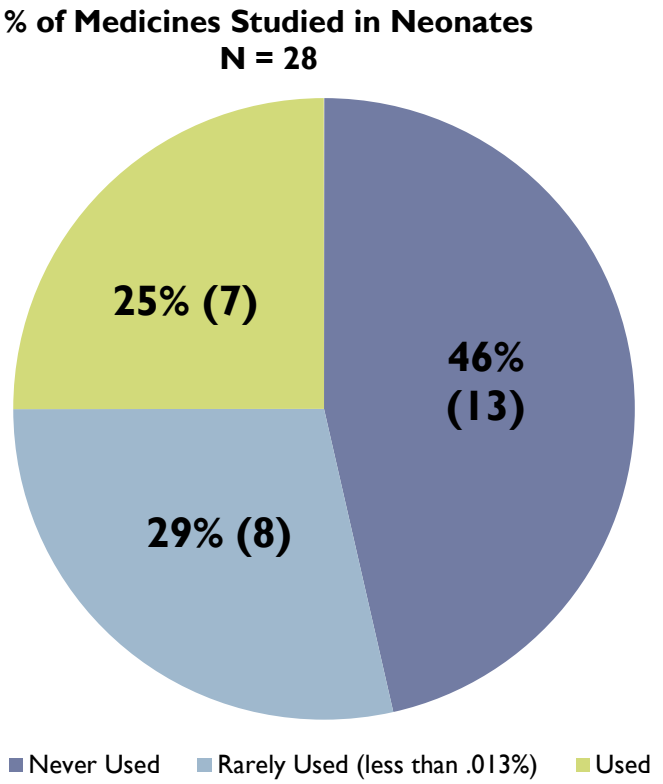
Scenarios of Drugs Evaluation in Neonates

- Off patent; off label drugs
  - Evaluation through academic studies
  - BPCA process (e.g. PTN) with industry assistance when possible; PUMA
- New drugs developed for adult purposes (Stiers)
  - Rarely used in neonates but assessed as part of regulatory process
- New drugs with potential indication for use in neonatal/infant population: becoming more common as part of or focus of rare disease/targeted focus
- Drugs that are needed in neonatal population: INC
  - Partnership of academia, industry, regulators
    - 6 priority therapeutic areas: brain, lung, GI injury; ROP, NAS, sepsis
- Studies of drugs specifically for neonates vs inclusion of neonates in wider pediatric study
  - If sub-population, what are goals of the trial?

Pediatric Labeling is Not Enough
Example: Studies in Neonates

Studies must be clinically relevant

- Of 406 medicines that were studied in the pediatric population in order to achieve 6 months of exclusivity, only 28 (or **7%**) had been studied in neonates[1]
- Of those 28 drugs, the majority are not used regularly in this vulnerable population[1]



[1] *Stiers, J., et al. Newborns, One of the Last Therapeutic Orphans to Be Adopted. JAMA Pediatrics, February 2014, volume 168, Number 2*

Case 1: Cryopyrin Associated Periodic Syndrome (CAPS): Targeting molecular pathways

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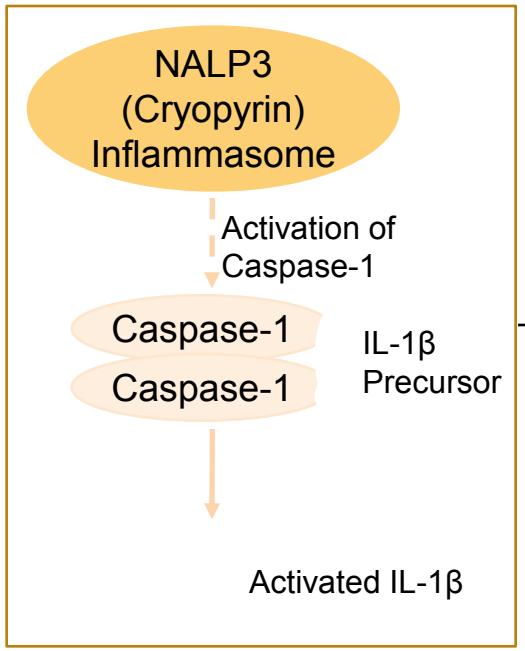
Pediatric Therapeutic Area

Understanding the Pediatric Disease Pathway Facilitates Development in More Common Conditions

IL-1β Pathway - abnormal signal transduction leading to disease

Pediatric Therapeutic Area

One pathway



High affinity, fully monoclonal anti-human interleukin-1β antibody of the IgG1/^{k} isotype binding human IL-1β blocking this cytokine's interaction with receptor.

One node

ILARIS (canakinumab)

Inflammation (IL-1β Pathway)

As of June 2013, 8,213 patients including 565 pediatric patients received this drug in sponsored clinical trials

Multiple diseases

- CAPS [1]
- SJIA [2]
- Chronic Gout
- CV Risk Reduction
- HPF [3]

[1] *Cryopyrin-associated periodic syndrome*
[2] *Systemic juvenile idiopathic Arthritis*
[3] *Hereditary Periodic Fevers*

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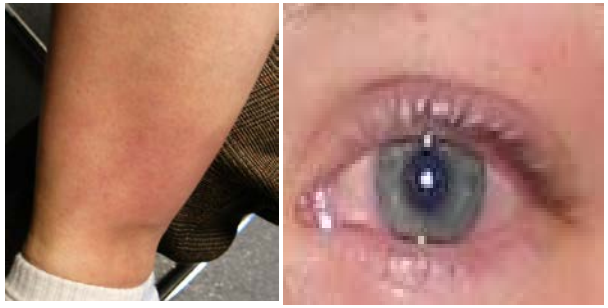
CAPS: Broad spectrum of diseases resulting from over-expression of Interleukin-1β

Pediatric Therapeutic Area

Cryopyrin Associated Periodic Syndrome (CAPS)

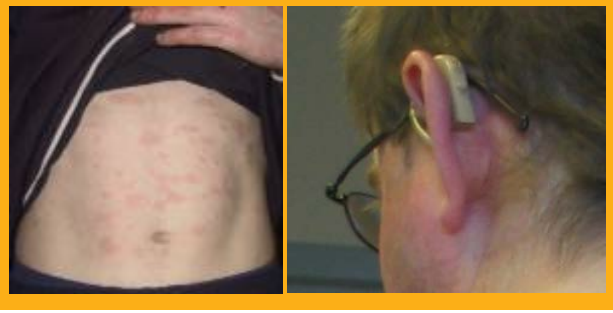
Mild



Familial cold autoinflammatory syndrome (FCAS)

- Autosomal dominant
- Rash, Arthralgia, Conjunctivitis

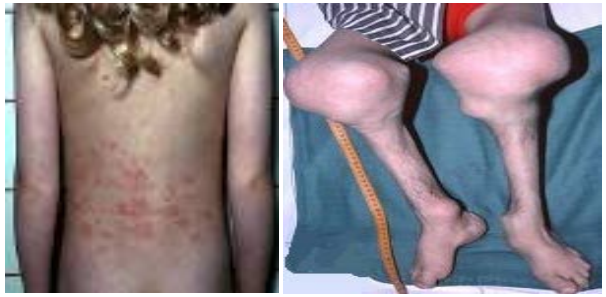
Moderate



Muckle–Wells syndrome (MWS)

- Autosomal dominant
- Rash, fever, fatigue, sensorineural deafness
- AA amyloidosis (in 25% of patients) leading to renal failure

Severe



NOMID/CINCA (neonatal onset multi-system inflammatory disease/chronic infantile neurologic, cutaneous articular syndrome)

- Sporadic (S331R mutation of CIAS1 gene)
- Progressive chronic meningitis, deafness
- Visual and intellectual damage
- Destructive arthritis

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Case 2: Spinal Muscular Atrophy: First in Infant approach to development

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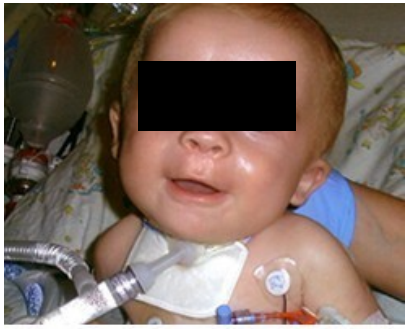
Pediatric Therapeutic Area

Spinal Muscular Atrophy (SMA)

Aligning internal and external stakeholders on a First in Child approach

Pediatric Therapeutic Area

https://clinicaltrials.gov/ct2/show/NCT02268552?term=LMI070+SMA&rank=1



- Autosomal Recessive disorder
- Most common genetic cause of infant death
- Pathogenesis of SMA due to functional loss of SMN1 gene
- SMN protein plays key role in motor neuron survival
- SMA subtypes with differential rate of motor neuron death
  - Type I most severe and most common (60%) form
  - Increased SMN2 copy number can partially rescue phenotype

SMA Type	Age at onset	Highest Function Achieved	Untreated Survival	SMN2 Copy #
Type I	0-6 months	Never sit	<2 years	2
Type II	7-18 months	Sit, never stand	>2 years	2 or 3
Type III	> 18 months	Stand and walk	Adult	4 or 5
Type IV	> 30 years	Walk as adult	Adult	> 5

* Type 0 SMA in-utero onset of motor neuron loss – symptomatic at birth babies

FPFV last week; publication of MOA of LMI070 in Nature Chem Biol next week

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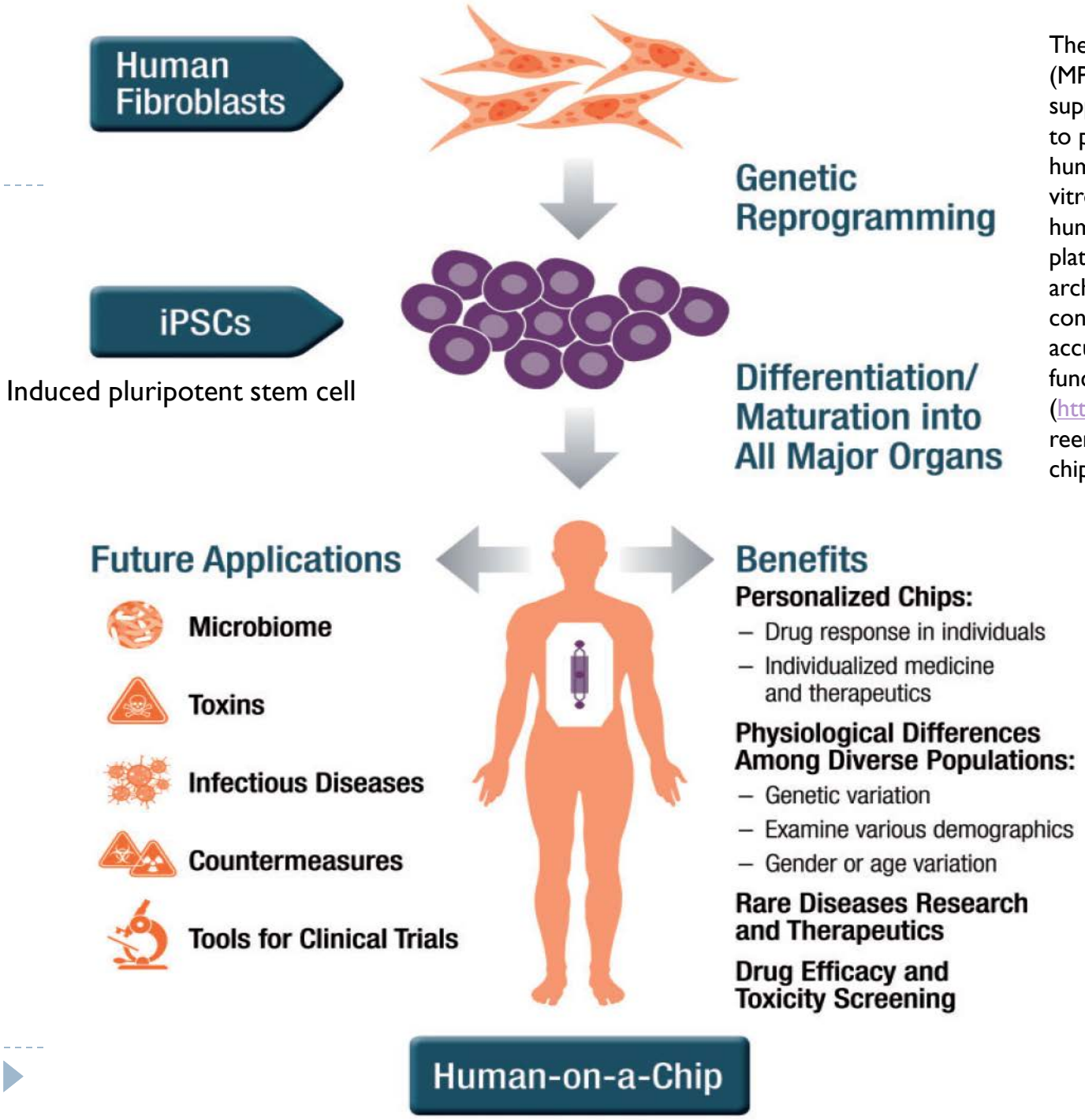
Priority Project Areas

- **Standardized methods and consensus-derived standards-of-care**
  - **Understanding natural history of disease and its therapy**
  - **Innovative study design (adaptive and Bayesian design)**
  - **Master protocols for multi-drug; multi-company studies (matrix design)**
- **Draft position papers** to assist the regulatory agencies in preparing guidance on the appropriateness of extrapolation of research results from other populations to the neonatal population, or from FT to premature, innovative trial designs (within patient studies)
- **Revised definition of neonates** to take into account physiology, etc.
  - **Particularly related to regulatory definitions**
- **Draft decision criteria for conducting clinical trials of new therapies**
  - **Clinical trial networks**
- **Drug Development Tools** endorsed or qualified by the regulatory agencies for a specific context of use. Such tools can also be used to evaluate interventions designed to prevent pre-term birth.
  - **Safety and Efficacy Biomarkers**
  - **Clinical Outcome Assessments (COA)**
  - **Modeling approaches such as physiologically based pharmacokinetic and disease progression models, as well as clinical trial simulation tools.**
- **Guidance on safer formulations**
- **AE and SAE reporting training**
- **Applying personalized medicine to the treatment of neonates.**

Innovations Needed for Successful Neonatal Drug Development

- All NICU patients should be treated through a research protocol similar to pediatric cancer patients
- High through-put screening for new drugs with developing cells as targets
- Opportunistic sampling not limited to off-patent meds
- Developmental changes in drug metabolism must be mapped more clearly through data from multiple drugs
- Innovative techniques for human toxicity assessment (organ-on-CHIP)
- Policy initiatives to stimulate innovation specific to neonatal need



The Microphysiological Systems (MPS) Program ("organs-on-chips") supports an innovative approach to preclinical toxicity testing on human tissue: development of in vitro, 3D organ systems from human cells on bioengineered platforms that mimic in vivo tissue architecture and physiological conditions in order to facilitate and accurately monitor key organ-level functions. (http://www.ncats.nih.gov/research/reengineering/tissue-chip/tissue-chip.html)

Conclusions

- Industry acknowledges obligations for drug development in the neonate/young infant population in partnership with academic and regulatory colleagues; focus should be on **opportunities and need**
- More information about this rapidly changing and heterogeneous population is required before effective drug development can be accomplished such as knowledge of
  - developmental drug metabolism
  - regulatory definitions of the neonatal population
  - validated end points and clinical outcomes
  - natural history of disease and evidence based standards of care
  - innovative trial designs
  - personalized medicine
- INC should provide guidance in developing needed tools and to serve as the coordinator of priorities for the first efforts in this area.
- These trials should be performed by a coordinated **global clinical trials network**
- Industry is leveraging the radical changes in science, medicine and technology to find new targets and novel ways to improve pediatric/neonatal patient outcomes
- Once found, beginning a new therapy during the newborn period may be the most effective timing for maximal benefit
- Evolving early decision and portfolio analysis accompanied by model based drug development and innovative clinical assessment are conduits for future pediatric drug development
- Policy initiatives to stimulate innovation specific to neonatal need

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The German Neonatal Network
Trial sites

- Cohort-study of preterm infants with a birth weight below 1500 grams
- Supported by the German Federal Ministry of Education and Research (2009-2021)

The German Neonatal Network (GNN) Patients

Typical complications

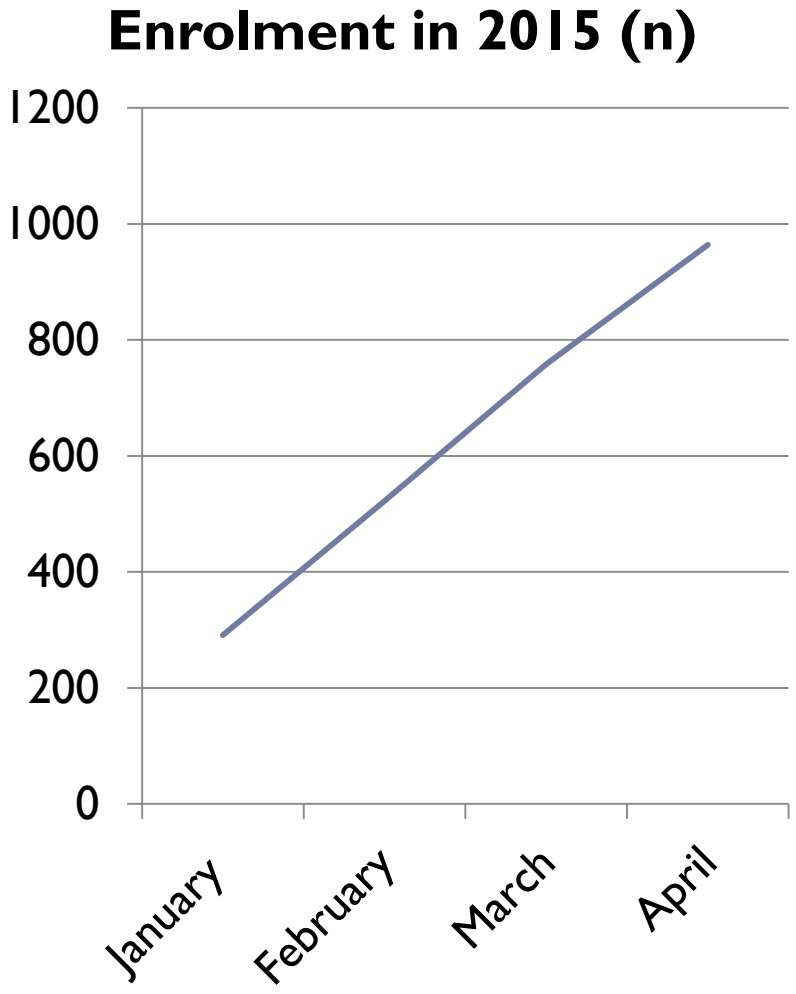
Until discharge:

- Surfactant treatment (Respiratory distress syndrome, 60%)
- Bronchopulmonary dysplasia (12%)
- Intracranial haemorrhage (18%)
- Sepsis (16%)
- Surgery for necrotizing enterocolitis (4.5%)
- Death (4%)

At 5 years:

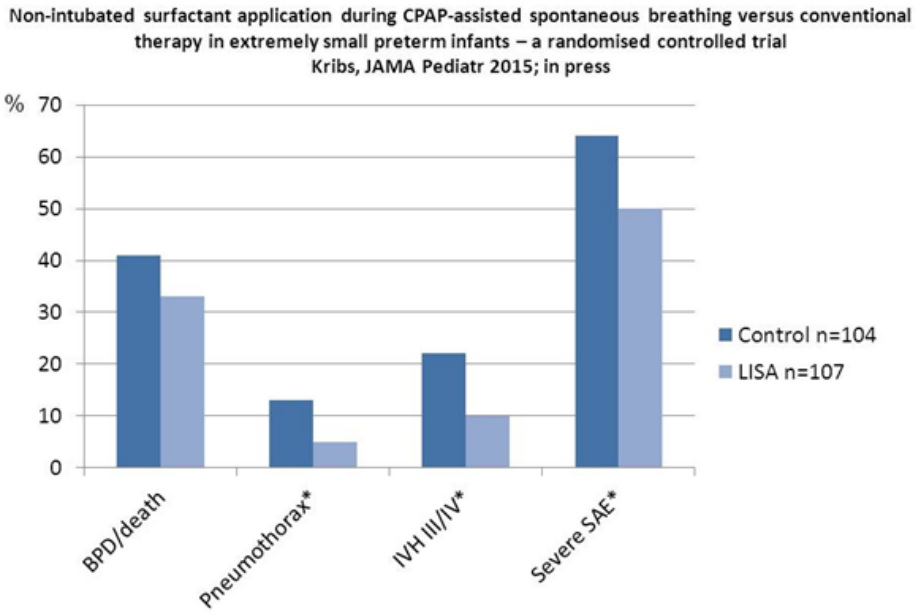
- FEV1 < 80% of predicted value (40%)
- Intelligence quotient < 70 (12%)
- Short stature (14%)
- Hearing loss (7%)

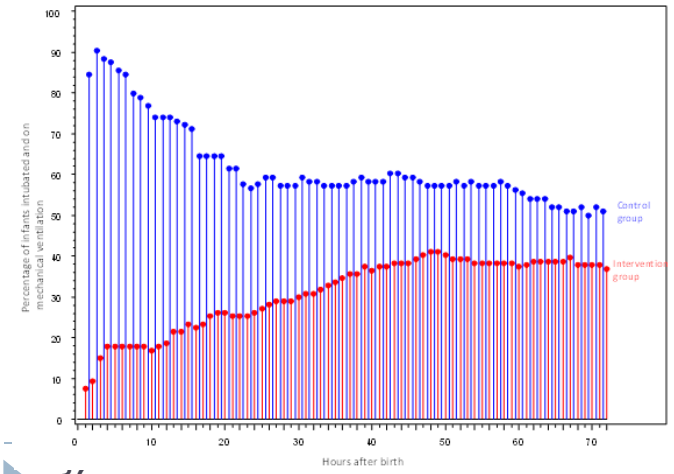
The German Neonatal Network (GNN) Biosamples



- Number of patients enrolled since 2009: n=11,474
- Current enrolment: 250 infants/month
- About 300 recorded items / infant during hospital stay
- Biosamples:
  - Infant-DNA (Buccal swabs, all infants)
  - Umbilical cord tissue (n≈9600)
  - Maternal DNA (n≈9800)
- Focus:
  - Clinical trials
  - Genetics
  - Long-term follow-up

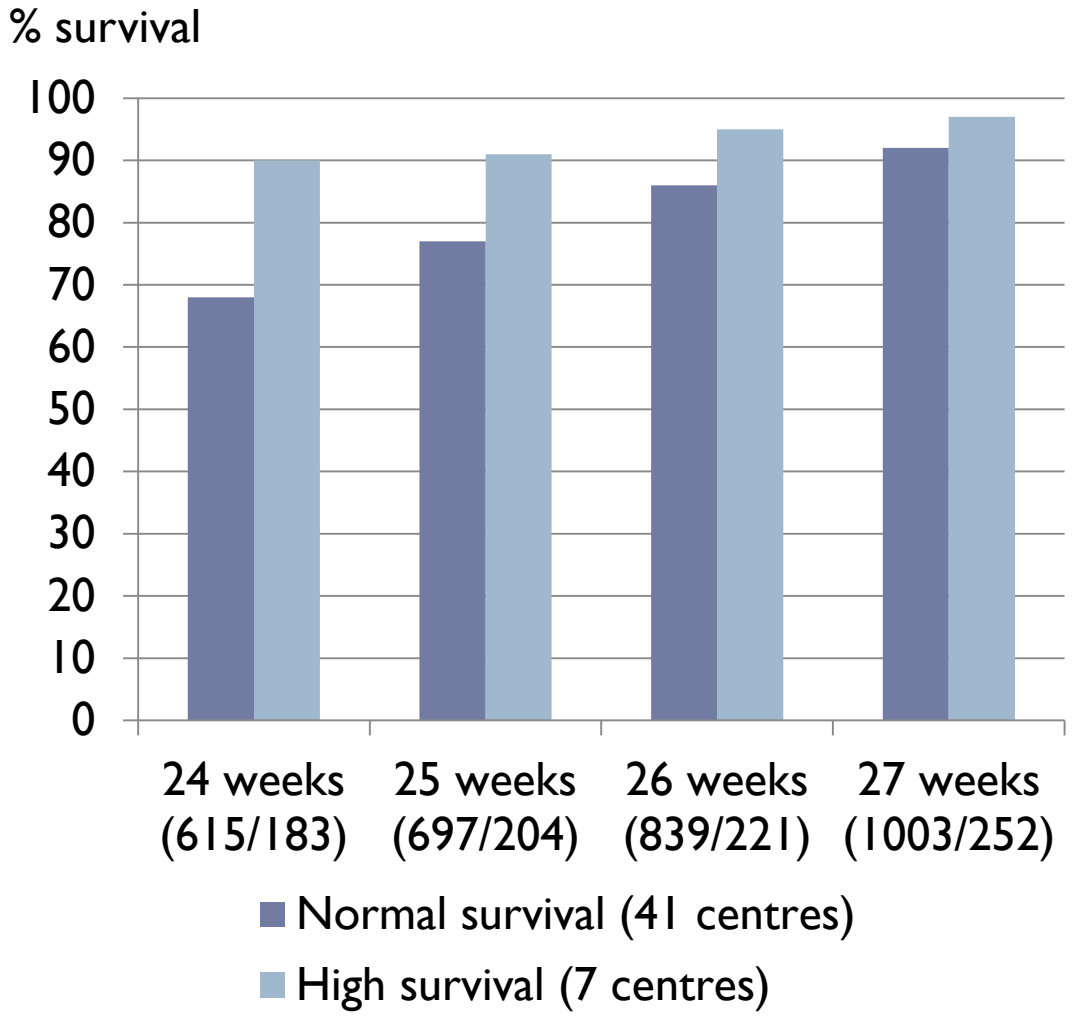
The German Neonatal Network (GNN): Clinical trials: Outcome





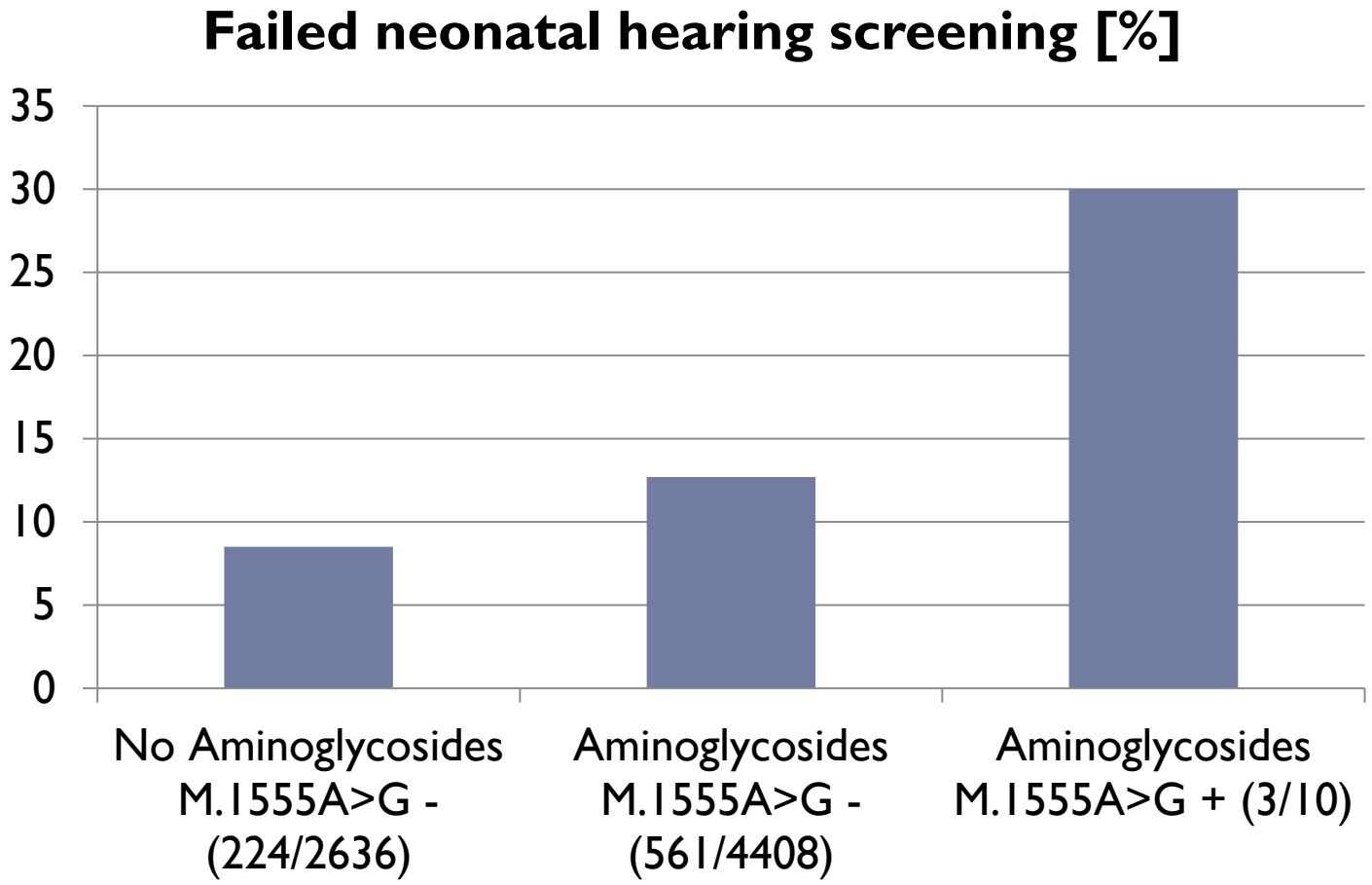
- Completed randomized controlled trials:
  - AMV: Less invasive surfactant administration (LISA) 26-28 weeks. Lancet 2011; 378:1627-34
  - NINSAPP: LISA, 23-26 weeks. Results will be published in June 2015 in JAMA-Pediatrics.
- Interventions in newborns (and especially in preterm infants) can induce unexpected benefits and harms.
- Standardized and complete outcome assessment will be very helpful for all stakeholders.

The German Neonatal Network (GNN): Clinical trials: Future



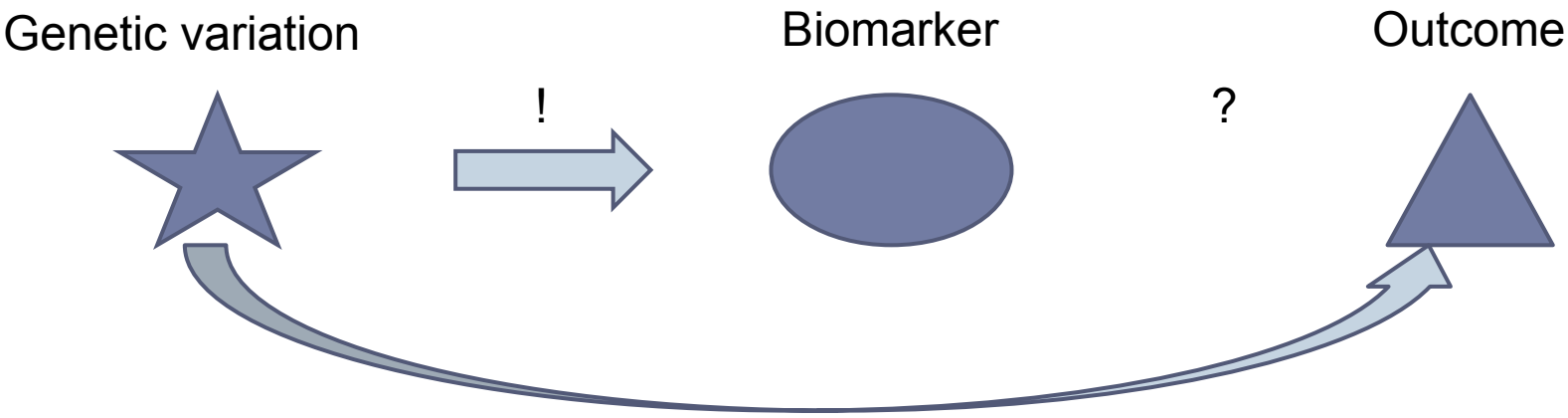
- Considerable between-hospital variation with regard to survival and treatment.
  - Improve standardization
  - NICU-patients should be treated according to protocols (like paediatric cancer).
- In addition to these very large trials and/or registers small RCTs for subgroups are needed.

The German Neonatal Network (GNN): Genetics: Pharmacogenomics



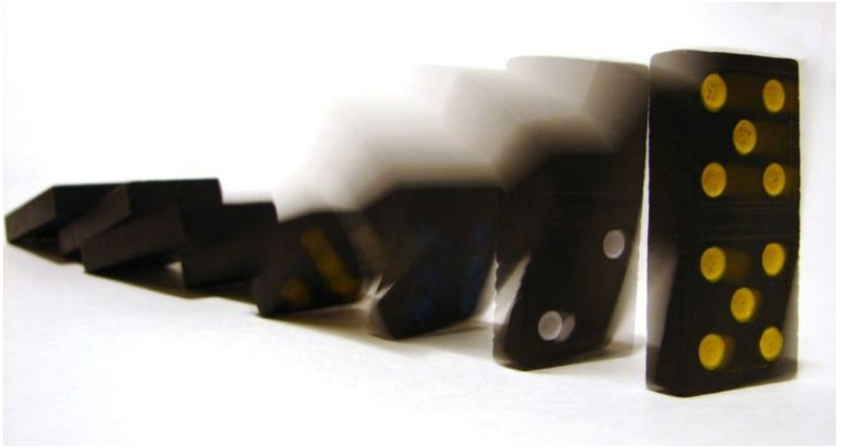
BMC Pediatrics 2014; 14:210

The German Neonatal Network (GNN): Genetics: Mendelian Randomization



If epidemiologists are compared with fishermen, causality is the big fish. It is elusive to find, difficult to catch, and claims to have measured it are often exaggerated.

But, despite the challenge, demonstration of causal relations remains a central aim of epidemiological inquiry.



Burgess, BMJ 2012;345:e7325

The German Neonatal Network (GNN): Genetics: Mendelian Randomization

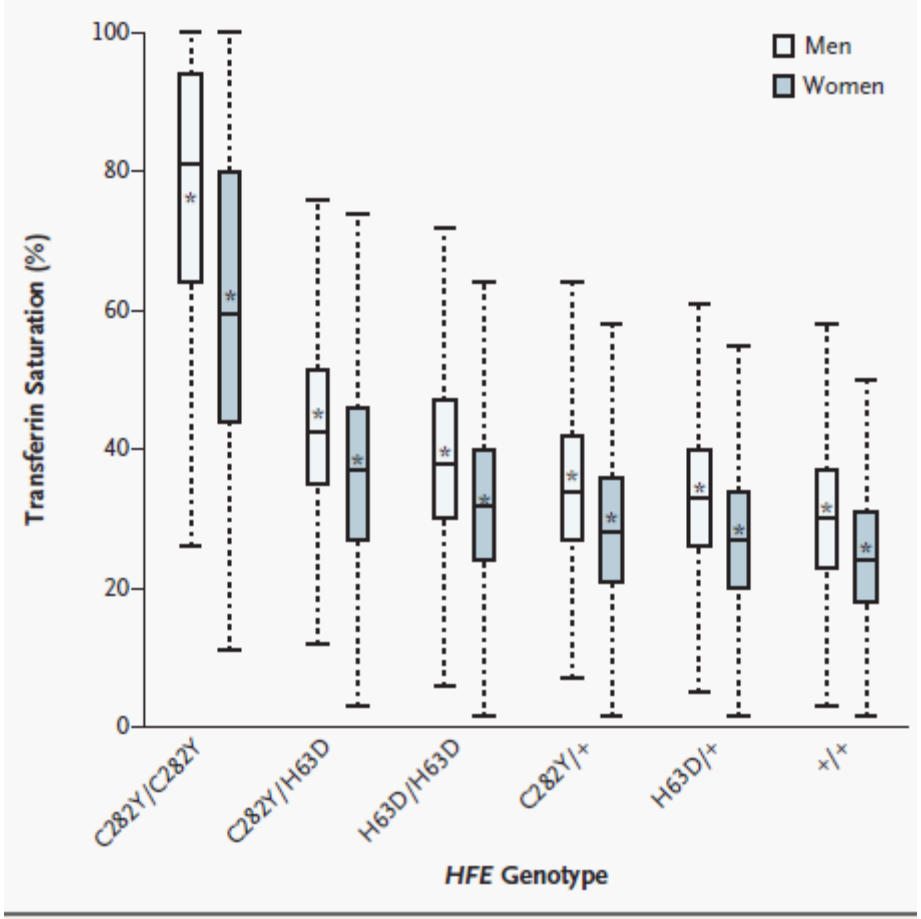
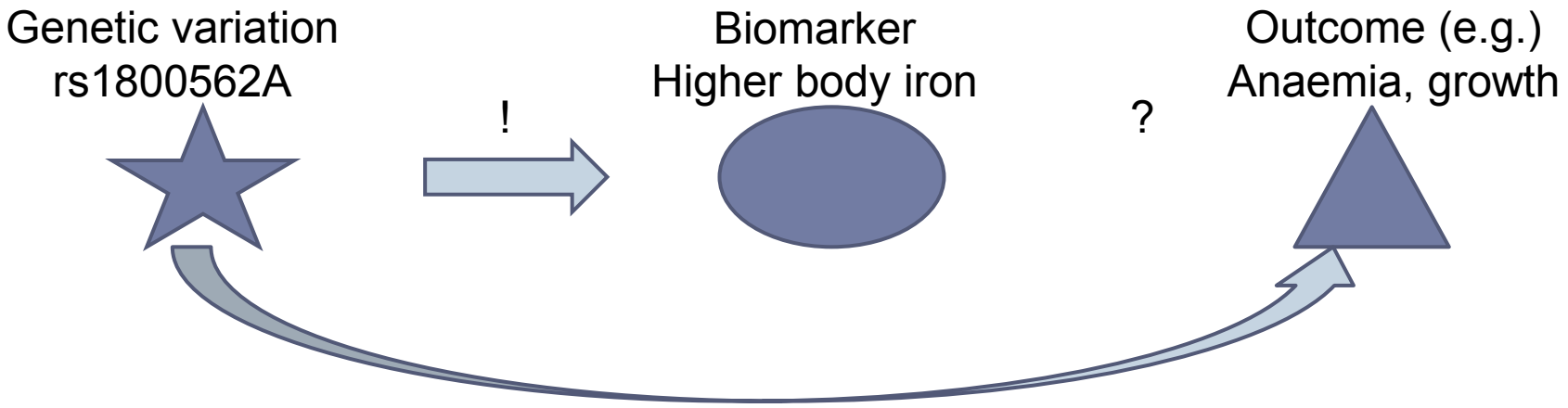


Figure 1. Nonfasting Serum Transferrin Saturation in Men and Women According to Genotype.

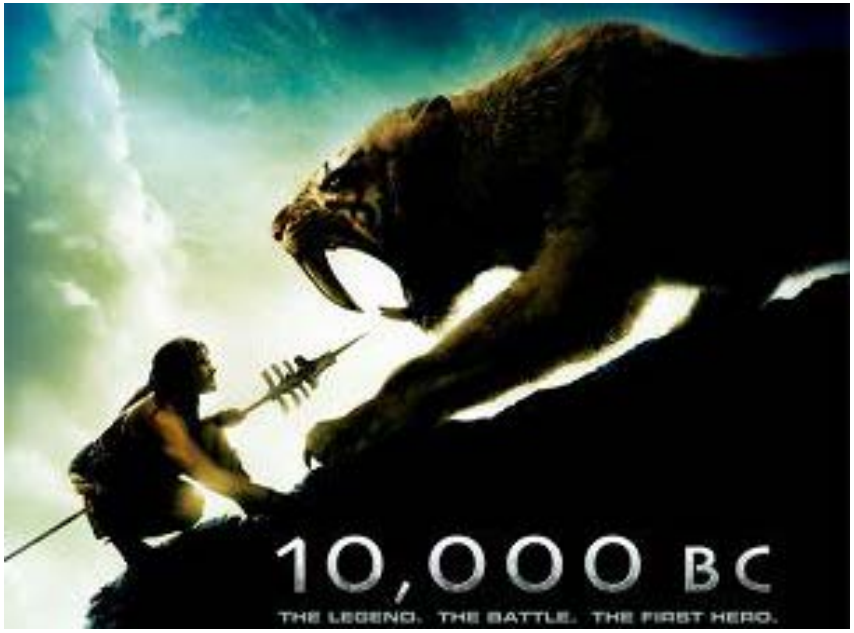
- Iron is a precious cellular metal, sequestered by hosts and scavenged by pathogens.
- About 10% of all persons of European ancestry carry the rs1800562-A (C282Y) polymorphism of the HFE-gene.
- They have higher transferrin-saturation and higher body iron stores.
- In Europe 0.4% are homozygous for the polymorphism and may develop iron overload and hemochromatosis.

Adams, N Engl J Med 2005;352:1769-78

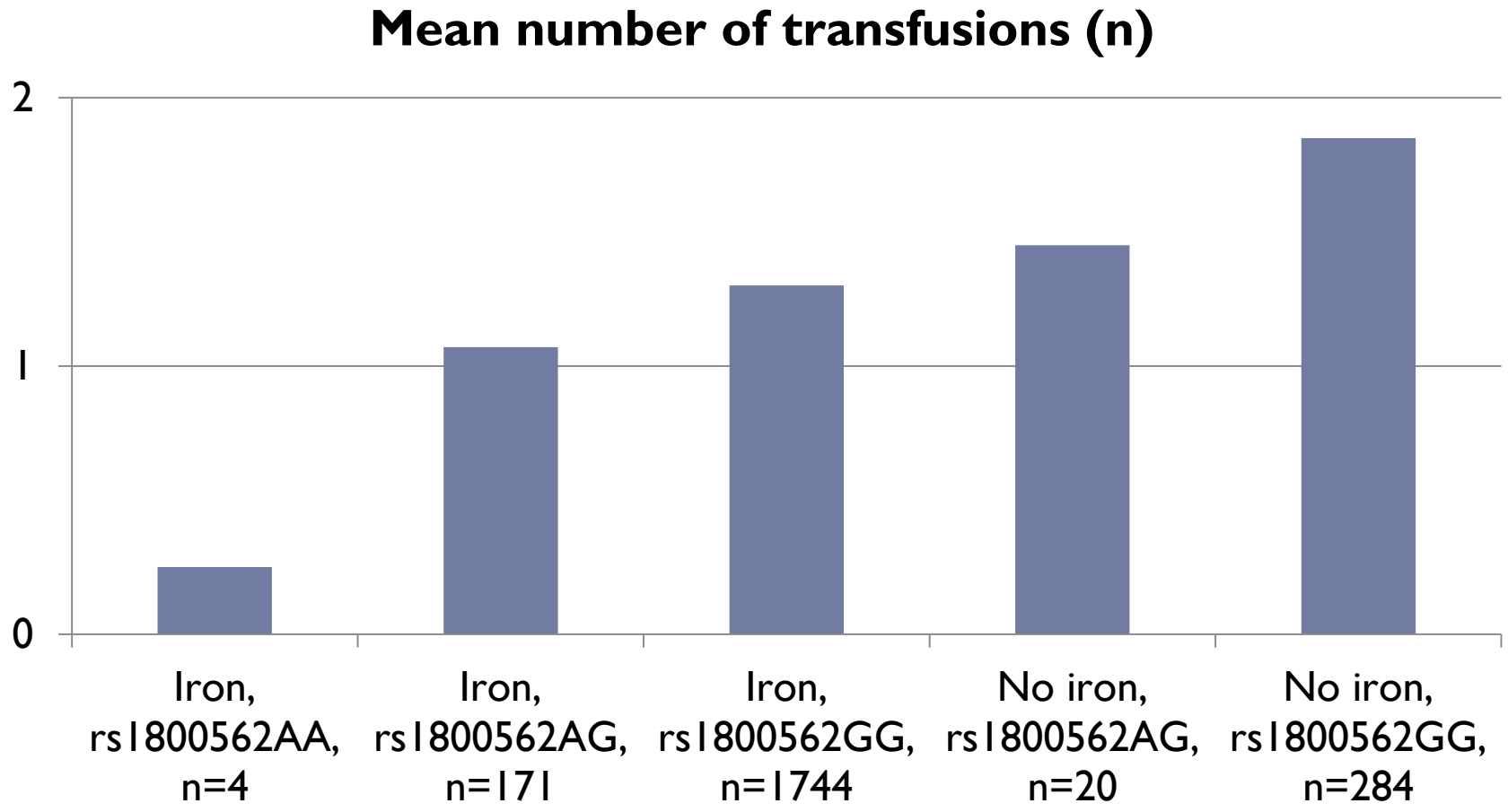
The German Neonatal Network (GNN): Genetics: Mendelian Randomization



- **The rs1800562A-genotype is comparable to a life-time iron therapy in a randomized controlled trial.**
- From a historical viewpoint, blood loss was much more frequent if compared to hemochromatosis.
- This genotype might be helpful for preterm infants who frequently need iron-supplementation and transfusions.

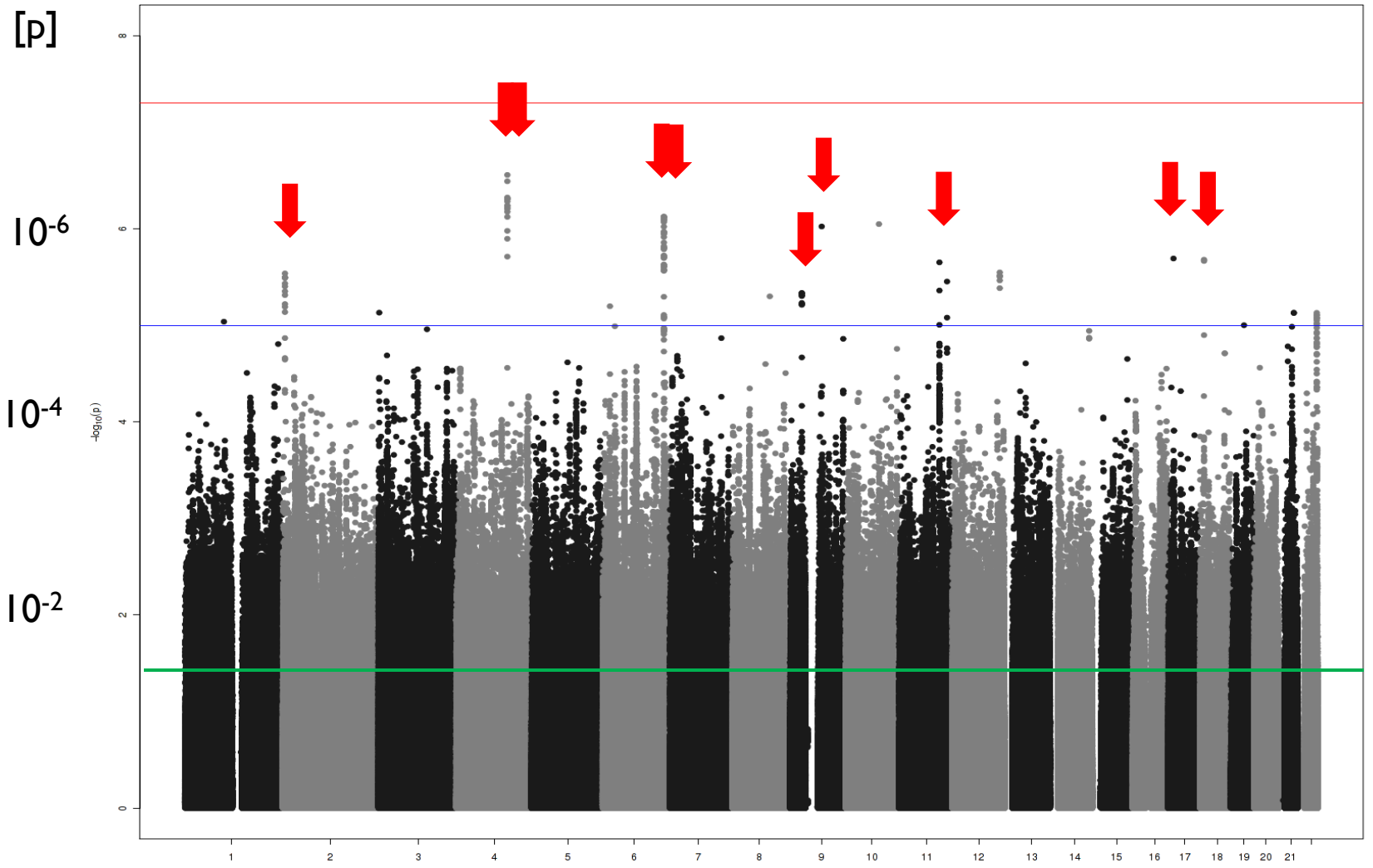


The German Neonatal Network (GNN): Genetics: Mendelian Randomization

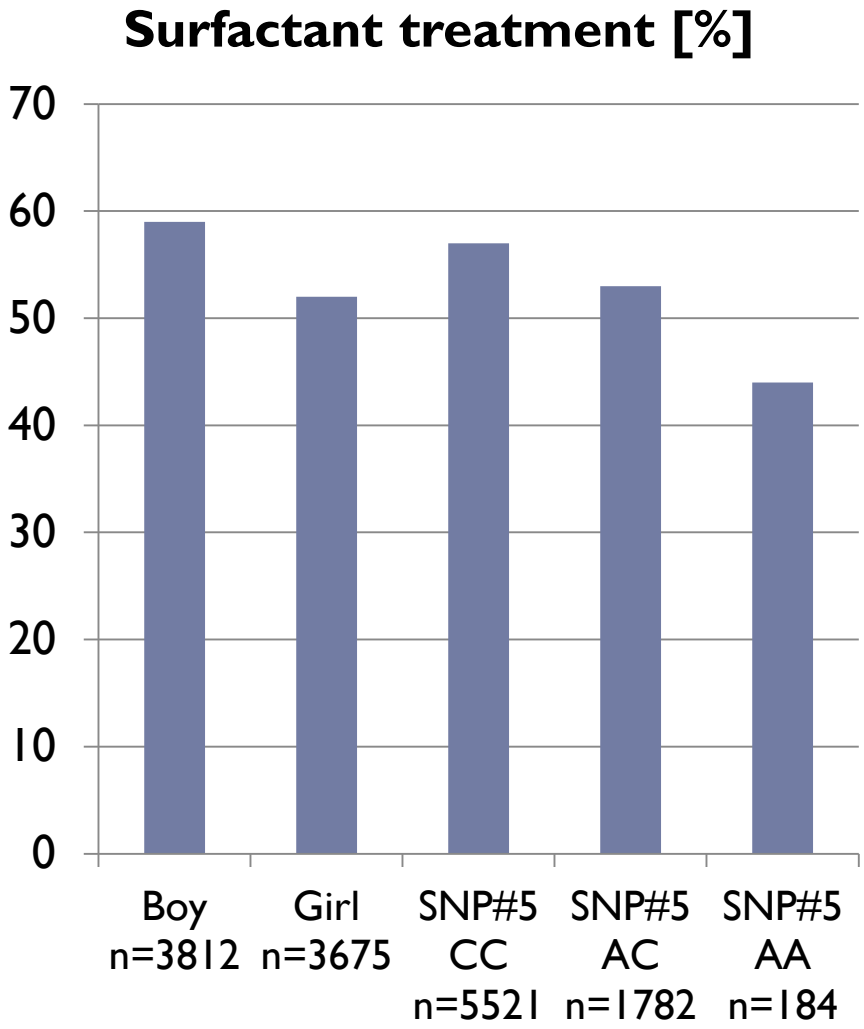


GNN, unpublished

The German Neonatal Network (GNN):
Genetics: Genome wide association (GWAS)



The German Neonatal Network (GNN): Genetics: GWAS



- Genome-wide association
  - SNP-chip-genotyping in 2250 infants completed
  - Planned total number until 2021: 10,000 infants
- Origin of GNN-participants
  - Germany: 75%
  - Other EU-countries: 10%
  - Turkey, Middle East: 8%
  - Asia: 2%
  - Africa: 5%

The German Neonatal Network (GNN): 5-year follow-up

- Parents are invited to their local trial site.
- One team, all instruments from GNN.
- Tests: 4 stages
  - Interview and spirometry
  - IQ-test (WPPSI III)
  - Anthropometric data, blood-pressure, audiometry, vision test
  - Neurological assessment, parents informed about results

The German Neonatal Network (GNN) Summary

- Neonatal intensive care teams (think of 50-100 persons/unit) are extremely trained and experienced to achieve measurable short term benefits for their patients.
- But they are often unaware of:
  - Long-term outcome of their own patients
  - Short- and long-term outcome of other units
  - Ways to improve the general outcome
  - Specific needs of infants with additional diseases/conditions.
- They need:
  - Large trials/registers for continuous improvement of therapy (similar to paediatric oncology)
  - Data on long-term outcome of patients (if possible external assessment)
  - Better diagnostic tools (biomarkers) and drugs for rare diseases and conditions.

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Moving Neonatology into the Modern Era of Drup Development: Overview of Potential consortium projects and deliverables

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International Neonatal Consortium

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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a decade of excellence
10 YEARS

Whence Neonatal Drug Development

- Stephen P. Spielberg, MD, PhD
  - Editor-in-Chief, Drug Information Association Publications
  - Former Deputy Commissioner for Medical Products, US FDA
  - Former Dean, Dartmouth Medical School
  - Pediatric Clinical Pharmacologist in academia and industry
  - Currently on advisory boards in pediatric therapeutics for Johnson & Johnson, Lumos, BMS, CASMI
  - Currently on Board of Trustees of the US Pharmacopeia

The Role of Therapeutics in Neonatal Outcomes

- Since the vast majority of morbidity, mortality, health care costs (short and long term) are attributable to prematurity, PREVENTION and a new focus on gestational therapeutics is warranted
- For the present discussion, fundamental issues include:
  - Basic understanding of the underlying mechanisms and pathogenesis of adverse neonatal conditions
  - Targeted drug development to address these
  - Clinical trial paradigms that support the needs of neonates and recognize the realities and complexities of such studies
  - Clinical trial networks and collaboration
  - Implementation of evidence in clinical practice

What Doesn't Work?

- Studying most newly approved NCEs approved over the last few years for adult indications with no associated neonatal rationale
- Repeated studies of drugs based on inadequate scientific rationale leading to poor study design/outcomes
  - The PPI story
    - Huge effort, huge costs, and huge lost opportunity costs for better basic understanding and for better studies
- Irrational usage patterns for drugs that have been studied
  - Pediatrics 135: 826-833 and 928-930, 2015
    - 40X variation in percent of neonates treated in 127 California NICUs with antibiotics (2.4-97.1%) with no differences in outcomes

What Does/Might Work?

- Scientific understanding leading to neonatal specific medicinal products
  - Surfactant
- Studies of interventions for inborn errors of metabolism
  - PKU, and now earlier interventions to prevent other phenotypes
- Studies of medications for adult/pediatric indications with thoughtful rationale of why and how to study in the newborn
  - International harmonization!!!
- Focusing on critical neonatal conditions associated with significant morbidity and mortality
  - The focus of this conference
- Bringing neonatal drug development into paradigms for other contemporary drug development
  - Targeted therapeutics based on molecular mechanisms
  - Genomics yes, but beyond

Uniqueness of Neonates

- Analogy to oncology targeted drug development
  - Susceptibility genes
    - BRCA, PG53 (Li-Fraumeni)
      - Germline mutations
  - Aberrant expression of drivers
    - Mutations, oncogenes, continuously changing in cancer cells, recurrences, metastases
- For neonates
  - Germline issues leading to increased (and decreased) risk for adverse lung, CNS, ocular, gut outcomes (maybe prematurity per se)
  - Developmental expression
    - Failure to express protective mechanisms
    - “developmentally abnormal” expression predisposing to damage from prematurity itself and our interventions

An International Neonatal Network Could/Should…

- Provide logistics for validation of potential biomarkers/"druggable" targets
- Validate biomarkers and end-points for clinical trials
- Study PK, PK/PD using validated outcomes
- Explore and optimize clinical trial designs to maximize new knowledge, and advise on ethics and practicality of studies
  - Obtain global regulatory buy-in
- Implement clinical trials of
  - Existing therapeutics drawn from adult/pediatric universe
  - Work in concert with basic and translational scientists in academe and industry towards discovery and development of true neonatal-specific interventions

The Future

- Amazing insights into human biology, driven in part by genomics (and other –omics)
- Opportunities to translate into previous unimagined interventions
- With large effect sizes, such interventions can be studied in small, novel clinical trials
- More rapid, efficient trial designs great for complexities of studies in neonates
- The need for global clinical trial networks has never been greater
- To improve public health, all sectors – academe, industry, regulatory, health care systems and financing, physicians in practice, and patients need expanded, novel ways of collaboration