INC
CRITICAL PATH INSTITUTE

International Neonatal Consortium

Second Annual Neonatal Scientific Workshop at the EMA

Welcome

September 12th – 13th, 2016

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Welcome Day 2

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at the EMA

Welcome to Day 2

Ralph Bax

September 13th, 2016

Agenda – September 13th

8:00 a.m.	**Welcome to Day 2** RALPH BAX (EMA)
8:15 a.m.	**Session IV:** *Precision Medicine for Neonates: Horizon Scanning* MARK TURNER (UNIVERSITY OF LIVERPOOL), CHAIR
10:00 – 10:30 a.m.	COFFEE BREAK
10:30 – 12:00 p.m.	**Session V:** *Long-term Outcomes* LEX DOYLE (UNIVERSITY OF MELBOURNE) & NEIL MARLOW (UNIVERSITY COLLEGE LONDON), CO-CHAIRS
12:00 – 1:00 p.m.	LUNCH
1:00 - 3:00 p.m.	**Session VI**: *Necrotizing Enterocolitis* RON PORTMAN (NOVARTIS), CHAIR
3:00 – 3:15 p.m.	*Concluding Remarks*, MARK TURNER, INC CO-DIRECTOR
3:15 p.m.	WORKSHOP ADJOURNED

Adding Predictability to the Regulatory Path: Potential Deliverables of INC

- Drug Development Tools endorsed or qualified by the regulatory agencies for a specific context of use:
  - 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.
- Develop standardized methods, master protocols, and consensus-derived standards-of-care.
- Draft white papers to assist regulators in preparing guidance on innovative trial design, appropriate extrapolation of research results, decision criteria for conducting clinical trials of new therapies, safer formulations encompassing ease of administration, etc.

Agenda – Precision Medicine for Neonates: Horizon Scanning

8:15 a.m.	**Session IV:** *Precision Medicine for Neonates: Horizon Scanning* MARK TURNER (UNIVERSITY OF LIVERPOOL), CHAIR **SESSION IV: PANEL** ANDY BHATTACHARJEE (PARABASE GENOMICS) WOLFGANG GÖPEL (UNIVERSITY OF LÜBECK) YONGCHANG QIU (SHIRE) THOMAS MORGAN (NOVARTIS) MARISA PAPALUCA (EMA) CYNTHIA POWELL (UNIVERSITY OF NORTH CAROLINA) STEPHEN SPIELBERG (DIA)
10:00 – 10:30 a.m.	COFFEE BREAK

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Precision Neonatology with NGS; Precision Medicine for Neonates: Horizon Scanning session

July 12-13th, 2016

Andy Bhattacharjee, PhD

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Test Development Challenges in Newborns

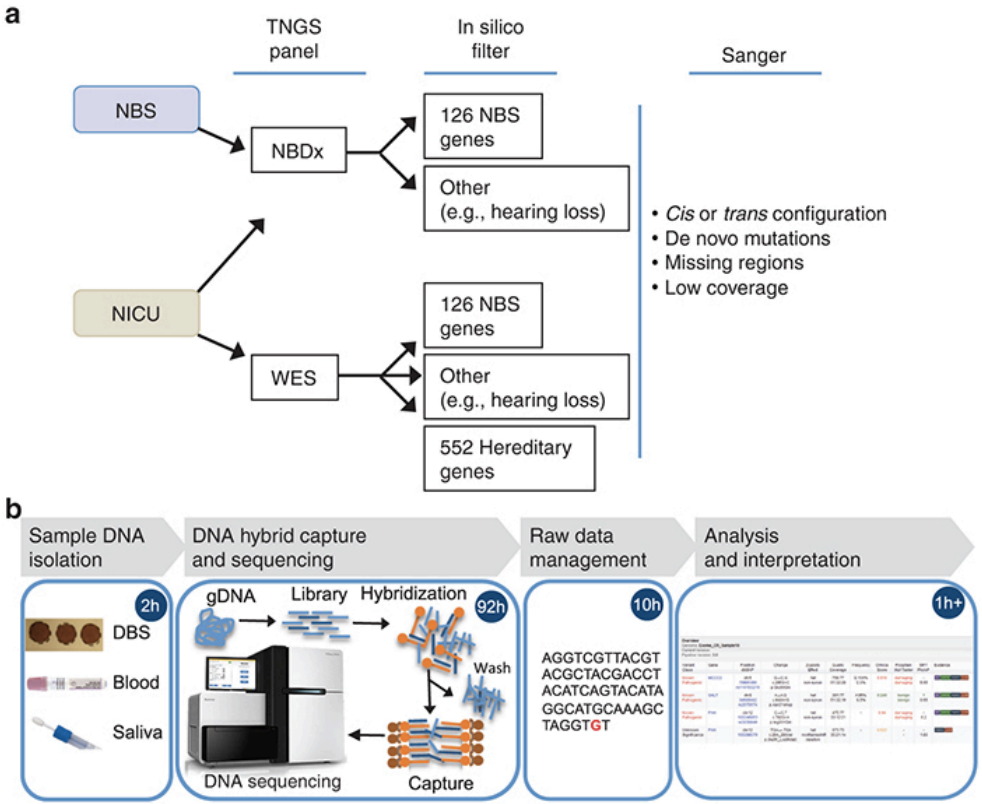
1) Optimal NGS Assays:
   - Ideal Gene panels to detect newborn genetic diseases
   - Fast turnaround times- <5days
   - Integrate NGS Assays with Copy Number Variation(CNV), homology/pseudogene removal and phasing techniques and intronic coverage
   - Expand DNA isolation protocols to minimally invasive samples <0.5mL

2) Build Ancillary Assays to complement neonatal differential diagnosis.

3) Develop other test opportunities in screening and well-baby testing for treatment

4) VUS variant qualification to expand universe of known pathogenic variants and reduce VUS readout, etc. This is a bottleneck and needs to be resolved. The human mutation rate, the rarity of diseases will necessitate a more intense collaborative model.

Newborn Disease Management



Sequencing in Symptomatic Newborns

Author	Site	# Patients	Method	Yield	Yield (Std Care)	Mgmt Change
Petrikin	Kansas City	35	Genome	57%	9%	65%
Stark	Melbourne	80	Exome	57%	13%	32.6%
Daoud	Ontario	20	Panel	40%	10%	25%

Petrikin: 45% of diagnoses made are conditions not considered in the differential

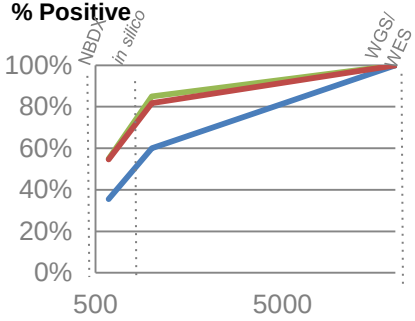
% Yield: NBDx Predicted Performance

	Gene	Predicted Coverage
Soden et al.NDD_NICU cases		
1*	*PTPN11*	NBDX1.1
2*	*PTPN11*	NBDX1.1
3*	*MTTE*	not targeted
4*	*SCN2A*	Parad extended NICU
5*	*KAT6B*	Hypotonia Extended
6	*SLC25A1*	NBDX1.1
7*	*KCNQ2*	NBDX1.1
8*	*GNPTAB*	NBDX1.1
9*	*SCN2A*	Parad extended NICU
10*	*CHD7*	NBDX1.1
11*	*BRAT1*	not targeted
Soden et al., NDD_All cases		
12	*GNAS*	NBDX1.1
13	*COQ2*	Hypotonia Extended
14	*TBX1*	Autopsy
15	*ASPM*	NBDX1.1
16	*MT ATP6*	Autopsy
17	*NEB*	Hypotonia Extended
18	*COL6A1*	Hypotonia Extended
19	*STXBP1*	NBDX1.1
20	*ARID1B*	Hypotonia Extended
21	*NDUFV1*	EM/Hypotonia E./Autopsy
22	*RMND1*	Hypotonia Extended
23	*PIGA*	Hypotonia Extended
24	*AHCY*	NBDX1.1
25	*MECP2*	NBDX1.1
26	*STXBP1*	NBDX1.1
27	*MAGEL2*	Hypotonia Extended
28	*KMT2D*	NBDX1.1
29	*TSC1*	NBDX1.1
Willig et al.,NICU (*)		
30	*LAMB2*	Hypotonia Extended
31	*FGFR2*	NBDX1.1
32	*GATA6*	Parad extended NICU
33	*PHOX2B*	NBDX1.1
34	*CHD7*	NBDX1.1
35	*ABCC8*	NBDX1.1
36	*PRF1*	Parad extended NICU
37	*GJB2*	NBDX1.1

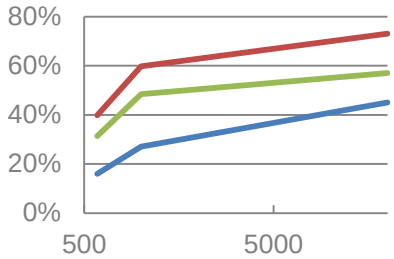
- 85% of NICU positive cases identified by a NBDX panel or an extended *in silico* set of genes.
- Genome scale approaches are best suited for clinically undiagnosed or perplexing conditions

	# Genes	NBDX 586	NB_in silico 1000	BabySeq_in silico 1724	WGS/WES 20000
Cases	NDD_All	16	27	32	45
	NDD_NICU	6	9	9	11
	NICU_Willig	11	17	17	20
% Positive	NDD_All	36%	60%	71%	100%
	NDD_NICU	55%	82%	82%	100%
	NICU_Willig	55%	85%	85%	100%
Diagnostic Rate	NDD_All	16%	27%	32%	45%
	NDD_NICU	40%	60%	60%	73%
	NICU_Willig	31%	48%	48%	57%

% Positive



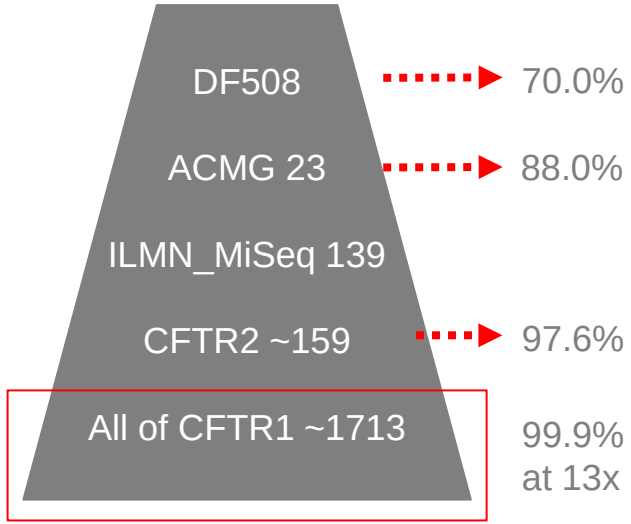
Diagnostic Rate

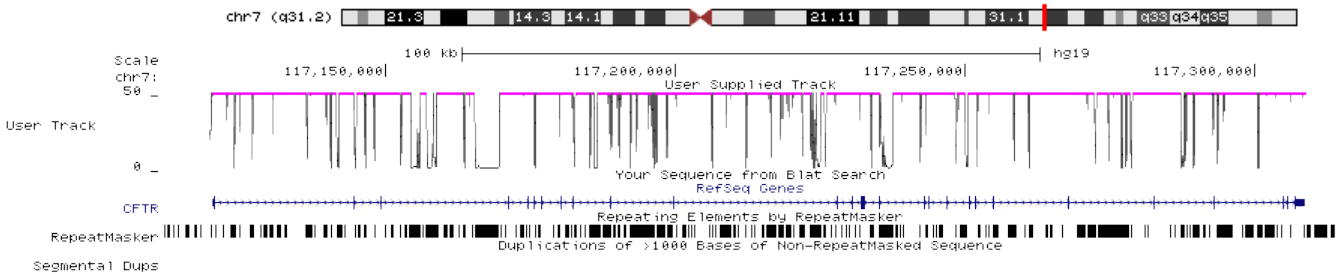


NGS Assay (CFTR viewpoint)

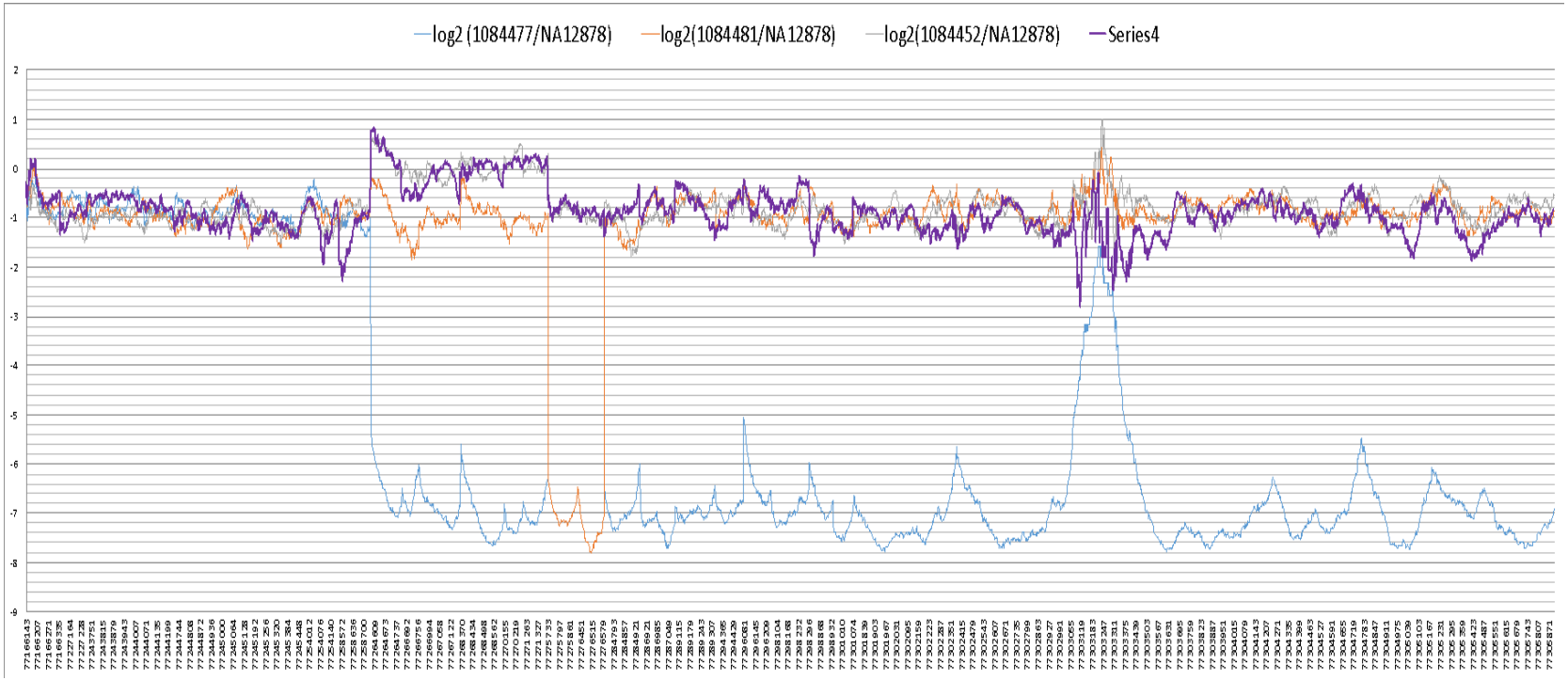
	CFTR Variants (n=1713)*	CFTR2 CF-Causing** (n=210)
≥ 20 reads	>99%	100%
≥ 13 reads	>99.9%	100%

*A standard exome (restricted to the coding exons) would have either number closer to 80% [based on Ensembl VEP annotation of 1713 variants].
**30 are splicing (+/- 10bp) and 3 are intronic





NGS Assay-CNV in Menkes Disease- ATP7A



Collaborator: Stephen Kaler, NICHD

Funded by: Menkes Foundation

Case #1

INITIAL DX: HYPERPHENYLALANINEMIA due to BH4 deficiency

Hx: hyperphenylalaninemia on newborn screen and subsequent testing suggestive of a defect in BH4 synthesis. 2nd tier testing included - QDPR gene sequencing. Treated with leucovorin, 5-OH-tryptophan, levodopa, carbidopa and sapropterin.

At 8 months, NBDx confirmed no QDPR variants. PAH revealed:

PAH Variant	Mother	Father	Classification
Missense c.782G>A/p.Arg261Gln	Het	Neg	Pathogenic
splice (rare) c.1200-1G>A	Neg	Het	Pathogenic

FINAL DX: PKU

IMPACT: Discontinued multiple medications (including some with significant risks)

Case #2

INITIAL DX: UNDIAGNOSED

Hx: Mother pregnant @ 14 wks gestation. 6 months prior had a term newborn who died suddenly @ 43h with hypoglycemia in WBN. Autopsy: severe fatty liver. Post-mortem NBS suggestive of FAO defect. Mat FHx + CF. NBS DBS retrieved. NBDx revealed:

CPT2 Variant	Mother	Father	Classification
missense	Neg	Het	Pathogenic
frameshift	Het	Neg	Pathogenic
CFTR Variant	**Mother**	**Father**	**Classification**
missense	Neg	Het	Uncertain
splice	Het	Neg	Pathogenic

FINAL DX PROBAND:
CPT2 deficiency/possible CF.
Amnio performed at 16.5 weeks. Fetus confirmed CPT2 carrier + 2 CFTR variants. Delivery pending.

SUMMARY

- NGS is well developed for utilization in newborns
- Precision medicine for newborns is possible
- NGS can improve management of phenotypes
- Meet newborn specific requirements
  - DBS, buccal
  - Lower cost of test
  - Trio Analysis
  - Reduce cost by integrating tests and serial testing
  - One stop shop or auto-reflex options
- Now that rapid TAT possible, care may be impacted
  - @ $5,000/day hospital charges may be diminished

REGULATORY CHALLENGES

- Newborns affected by genetic causes do not have precise testing that connect them to therapy.
- Newborn testing sample requirements remain unadapted. Poses a burden to studies that are burdenend by requirements.
- Diagnostic testing may involve multiple technologies and assays for differential diagnosis. So standards or algorithms are hard to standardize.
- Newborn diseases are rare -> large study cohorts need. The endpoints have to justify economic and clinical benefits for payors. Individual hospital based database records are small and have limitations. Multisite study difficult.
- Newborns do not show clear disease symptoms of a disease as the phenotype ‘is rolled out’. Thus test definitions and scope of use are complex.
- Several regulatory agencies like CMS (CLIA88)/CAP have exact analytical metrics as proposed by FDA.

REGULATORY CHALLENGES

Summary:

- FDA legislation at this point is too early and will basically eliminate or severely delay testing.
- Placing a moratorium or exempting newborn testing from FDA regulation surrounding NGS and germline genetic testing which is broad. Enable existing framework such as CLIA/CAP in the near term.
- Undertake or fund studies that investigates
  - impact of regulatory science on development of newborn precision medicine field via surveys
  - impact of standards on test development and outcome-specific for newborns

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Selecting promising therapies for preterm infants by Mendelian randomization

Wolfgang Göpel

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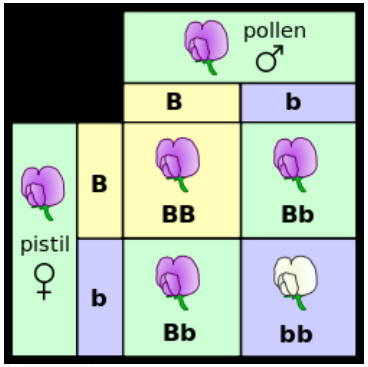
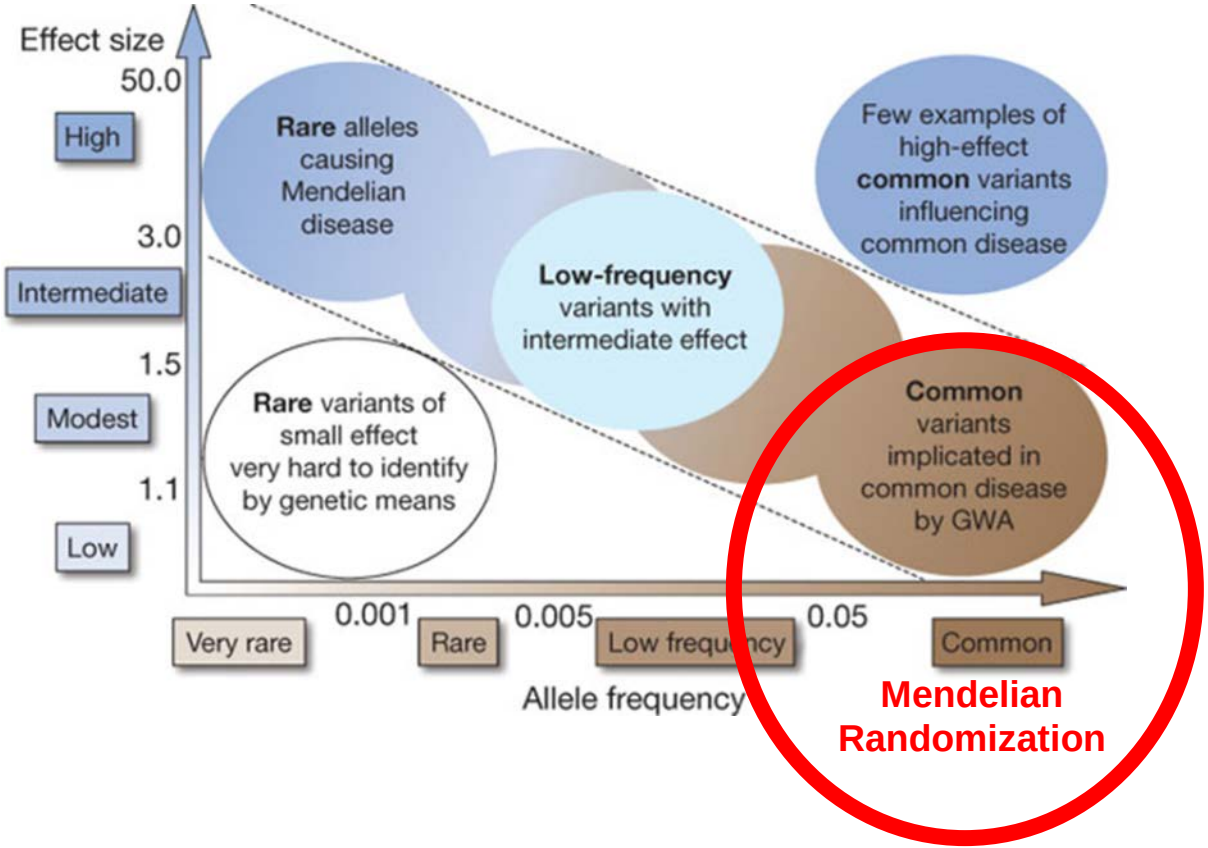
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mendelian randomization vs. Mendelian inheritance

Mendel‘s law of segregation

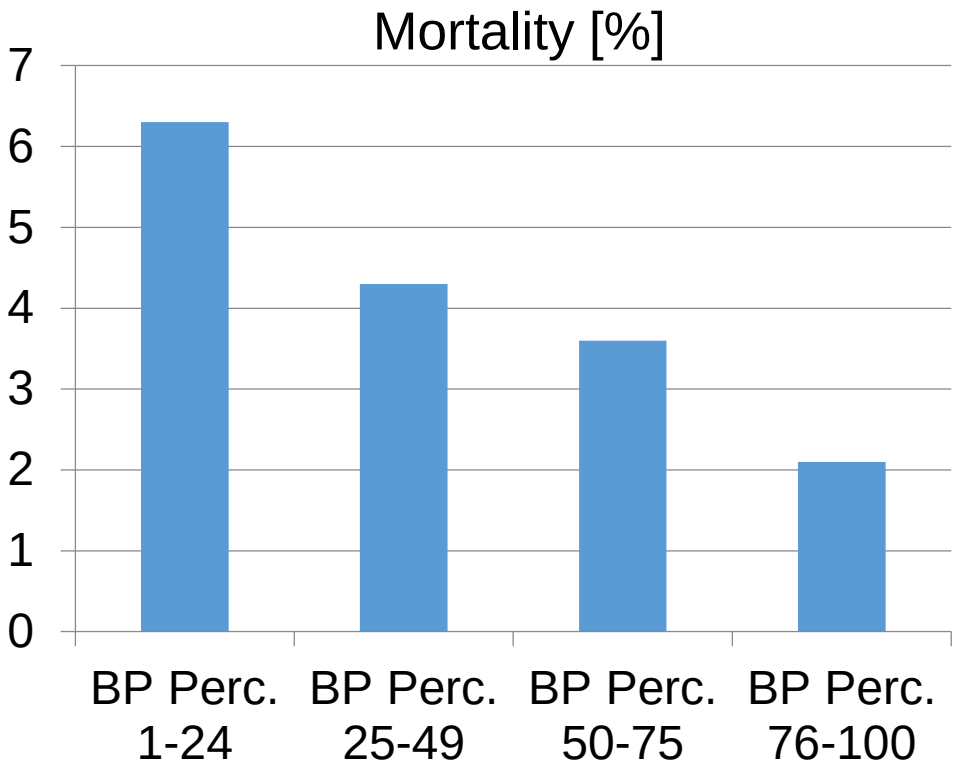


Gregor Mendel (1822-1884)



Wikipedia; Nature 2009; 461:747-53

A typical problem at the neonatal intensive care unit: Is the biomarker “low blood-pressure” predictive for death of preterm infants??



- Lowest blood pressure percentile (BP Perc.) on the first day of life and mortality until discharge in VLBW-infants (2009-2013, n=4907).
- Although the association is significant, low blood pressure might be not causal for death.
- The association might be due to confounding (e.g. infants with intracranial hemorrhage might have lower blood pressure).
- Mendelian randomization can prove causality.

Faust, Arch Dis Child Fetal Neonatal Ed. 2015; F388-92

Calculation of genetic estimated blood pressure

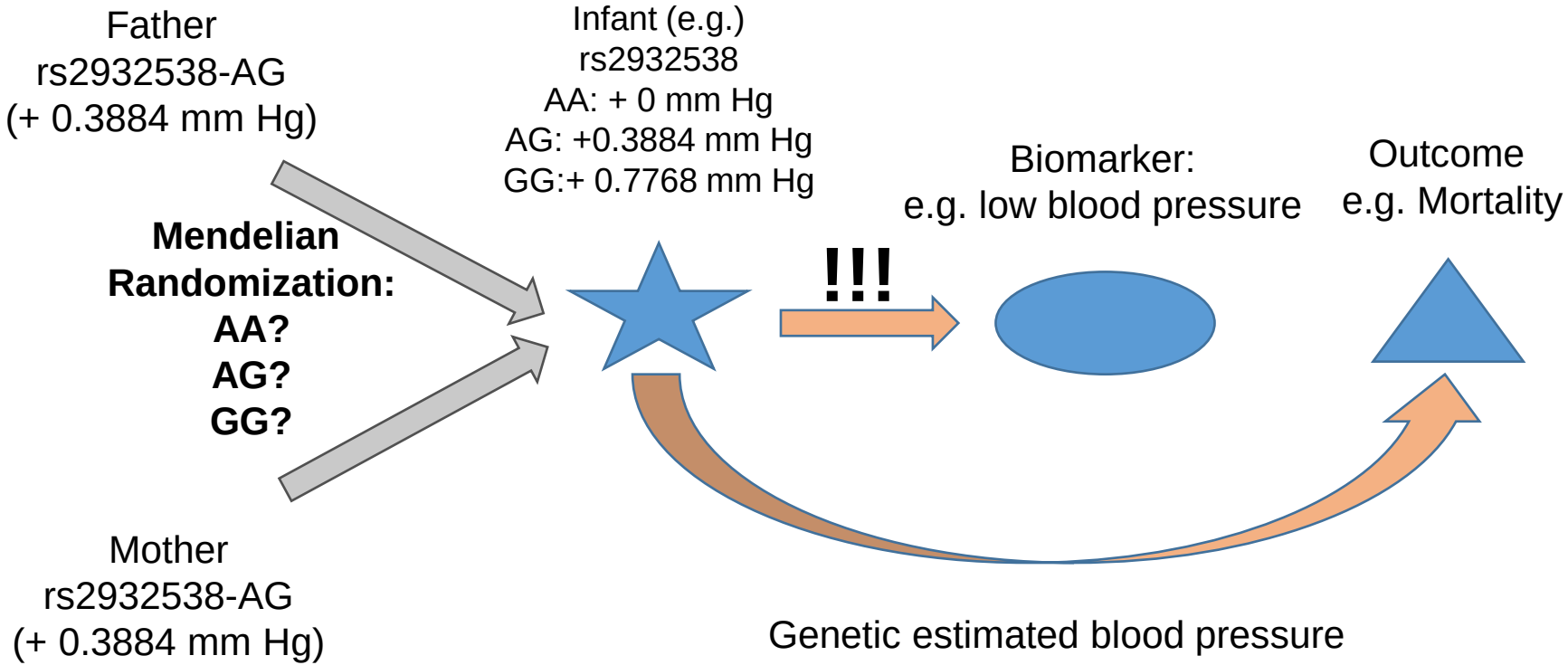
Increased blood pressure (per allele in mm Hg):

- rs2932538-AA: + 0 mm Hg
- rs2932538-AG: + 0.3884 mm Hg
- rs2932538-GG: + 0.7768 mm Hg

Trait	SNP	Nearest/nearby gene	Trait-raising allele[a]	Trait-lowering allele[a]	Beta for weighting genetic score
Blood pressure	rs2932538	*MOV10*	G	A	0.3884
Blood pressure	rs13082711	*SLC4A7*	C	T	0.3151
Blood pressure	rs419076	*MECOM*	T	C	0.4088

JAMA 2016; 315:1129-40

Mendelian Randomization



Genetic estimated blood pressure and blood pressure of preterm infants at 5 years

	Low (<P25) n=85	Intermediate (P25-75) n=137	High (>P75) n=62
Genetic estimated blood pressure [mm Hg]	Ref.	+ 1.8	+ 3.4
Systolic blood pressure at 5 years [mm Hg] 1. measurement *	100.5 ± 9.7	102.8 ± 9.0	103.7 ± 9.7
Systolic blood pressure at 5 years [mm Hg] 2. measurement *	98.3 ± 8.3	100.6 ± 9.5	102.1 ± 9.1

- Calculation based on 19 genetic markers (polymorphisms).
- Close correlation between genetic estimated blood pressure and blood pressure measurement at 5 years.
- Genetic estimated blood pressure can be used as a biomarker.

* $p<0.05$;T-test; Monatsschr Kinderheilkd; 2016; 164:668-672

Biomarkers eligible and challenges in infants

Mendelian randomization studies in adults used as genetic estimated instrumental variables:

- Blood pressure
- Forced expiratory volume in the first second, FEV1
- Plasma iron levels
- Body mass index
- Plasma vitamin D levels
- Plasma C-reactive protein levels
- Glomerular filtration rate
- …

Challenges in preterm infants:

- Quantitative effect data of single alleles are available in adults and (sometimes) in children, but not in preterm infants.
- Biomarker measurement (usually protein levels) is difficult in preterm infants due to the limited amount of blood/plasma for research.
- Some alleles are associated with more than one biomarker (pleiotropy).

Selecting promising therapies for preterm infants by Mendelian randomization

Summary

- Very few predictive biomarkers for diseases of preterm infants are published, since large scale biomarker-testing is not possible in this population due to the fragility of the patients.
- Mendelian randomization studies can be used to estimate the effect of biomarkers (like blood pressure) on relevant outcomes (like mortality) and prove causality.
- If a biomarker is causal and can be modified by a drug, this drug might be an interesting choice to modify the outcome.
- Since genetic variations can be easily measured in preterm infants, this approach will be very helpful for selection of promising therapies in the future.

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Development of pharmacodynamic biomarkers for IGF-1 supplement therapy in pre-term infants

Yongchang Qiu, Ph.D.
Bioanalytical & Biomarker Development, Shire

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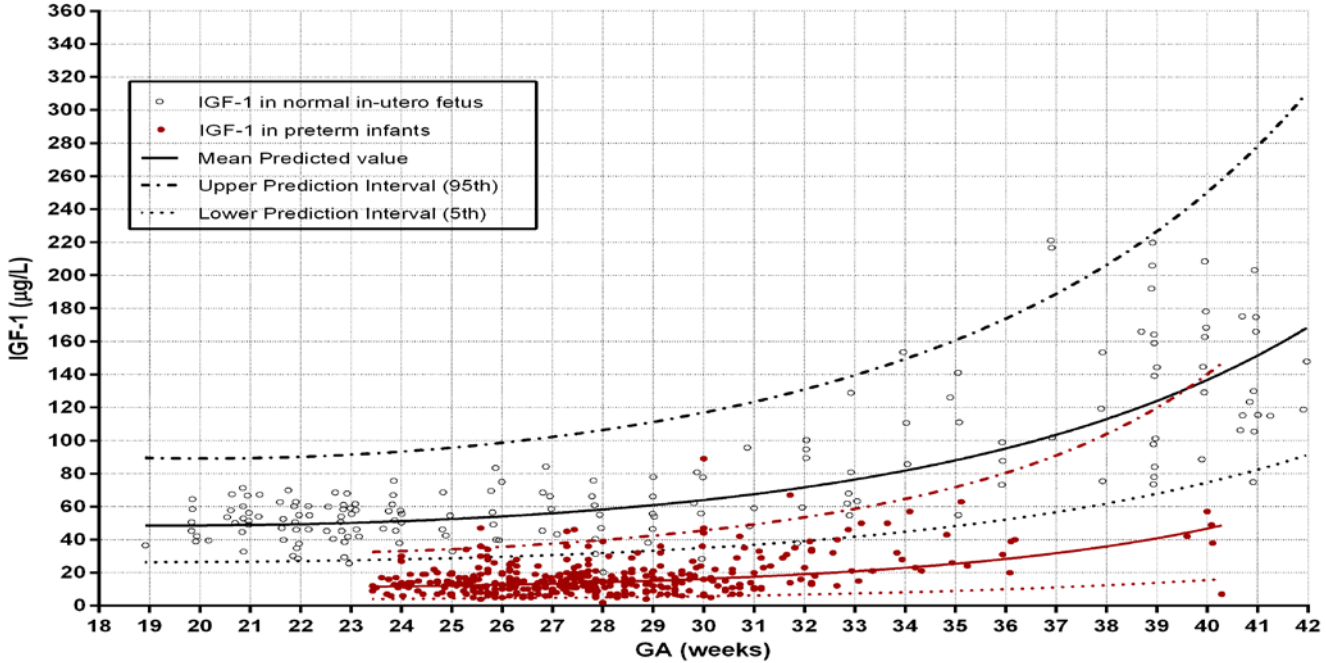
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DISCLOSURE

- Yongchang Qiu is a full-time employee of Shire

IGF-1 blood concentrations are significantly lower in preterm neonates than in normal in-utero fetus



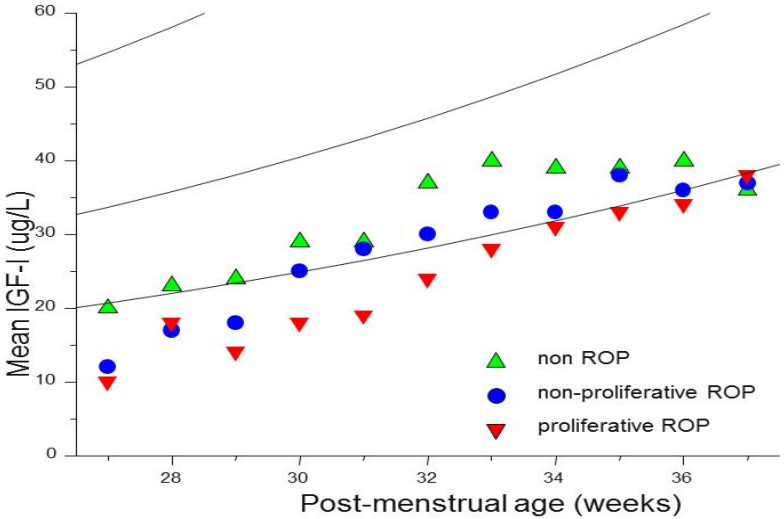
Mean fetal blood IGF-1 concentrations (samples obtained by cordocentesis from normal pregnancies measured by RIA) double from 18 to 42 weeks gestational age (GA) (n=174)). data from Lasarre et al and Bang et al. on IGF1 levels in utero.

Lasarre et al Pediatric Res. 36:528, 1994
Bang et al al Pediatric Res. 29:219, 1991

The level of IGF-1 deficiency is highly correlated with the severity of many neonatal complications (ROP, BPD, IVH, NEC, etc)

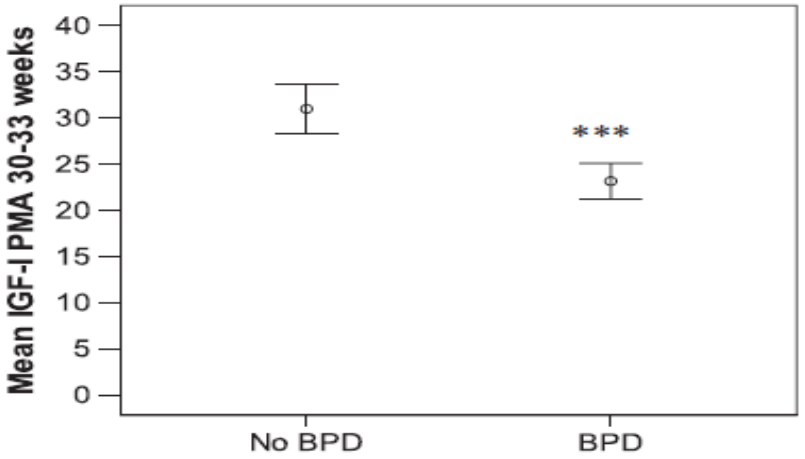
Retinopathy of Prematurity (ROP)

*Hellström et al PNAS 2001 98,*5804–5808



Bronchopulmonary Dysplasia (BPD)

Löfqvist et al Acta Pædiatrica 2012 1211–1216



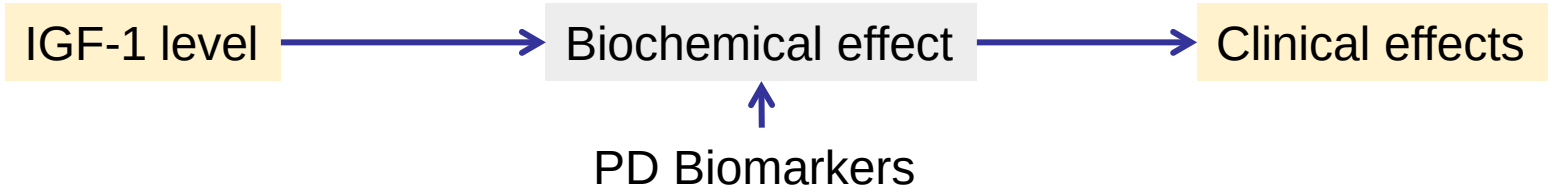
***P<0.001

Supplement of IGF-1 as a therapy for neonatal complications

- Top-line analysis of secondary endpoints showed clinically relevant effects on severe complications related to lung and brain damage

-- PR Newswire, June 30th, 2016

Complications	%reduction (overall)	%reduction (patients who achieved the pre-specified target IGF-1 levels)
Bronchopulmonary Dysplasia (BPD) (O2 challenge test)	53%	89%
Intraventricular hemorrhage (IVH) (Grade III and IV on centrally read ultrasounds)	44%	64%



Challenges on development of pharmacodynamic biomarkers for trials on neonates

PD biomarkers are critical for decision making (selecting patients for trial or treatment, confirming drug action, and dose optimization, etc.) but the protein biomarker knowledge base for neonatal complications is very limited due to:

- **Limited clinical sample type** – Blood is the only practical sample choice (Urine, CSF, tissue biopsy unlikely)
- **Very limited sample amount** – <3% TBV within 4 weeks and <1% TBV any one time draw (EMA guideline, 2009)
- **Technical challenges in protein profiling -** Given 20 uL serum sample, only a few analytes can be assessed using conventional bioanalytical means

Candidate Biomarkers for neonatal complications based on literature research

Bronchopulmonary Dysplasia (BPD)

Condition	Biomarkers
Inflammation	IL6, IL8, IGFBP-1
Angiogenesis	VEGF
Growth/ROP	C-peptide, insulin, Adiponectin
Neurotrophic factor	BDNF
Renal function	Cystatin C, NGAL, KIM-1, IL-18
Lung injury	KL6, CC16, ICAM-1

Ishizaka et al, Am J Physiol Lung Cell Mol Physiol 286:L1088 2004
Karger et al, Neonatology 93:223 2008.
Wang et al, Disease Markers, volume 2014
Ogihara et al, Ped Res 60:613 2006
Rozycki, Paediatr Respir Rev 14:173-179 2013.
Kozyrskij et al, J Matern Fetal Neonatal Med 15Aug epub 2015

Intraventricular hemorrhage (IVH)

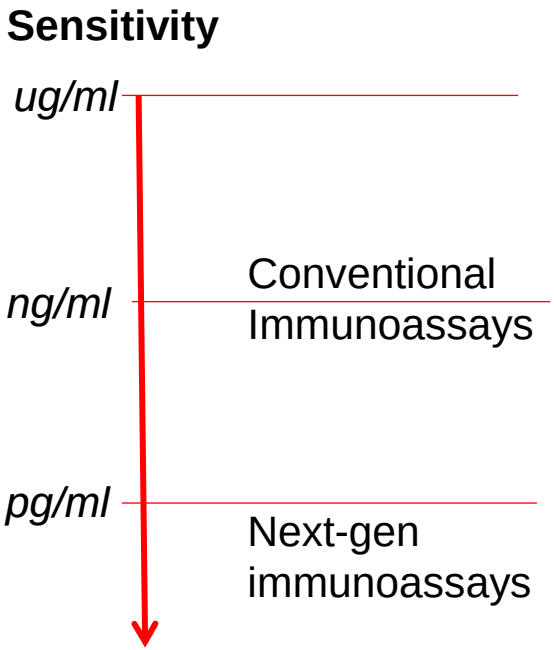
Biomarker	Physiological Role
IL-6 (blood)	Proinflammatory cytokine
Activin (blood & urine)	growth factor
S100b (blood & urine)	Astrocyte Ca+ binding protein
Adrenomedullin (blood)	cerebral vasoactive peptide

Int J Dev Neurosci 36:25-31 2014

Most candidates listed here are from research in children or adult patients rather than neonates

Technologies for measuring multiple biomarkers in limited blood or serum (<10 uL) at pg/ml level are now available

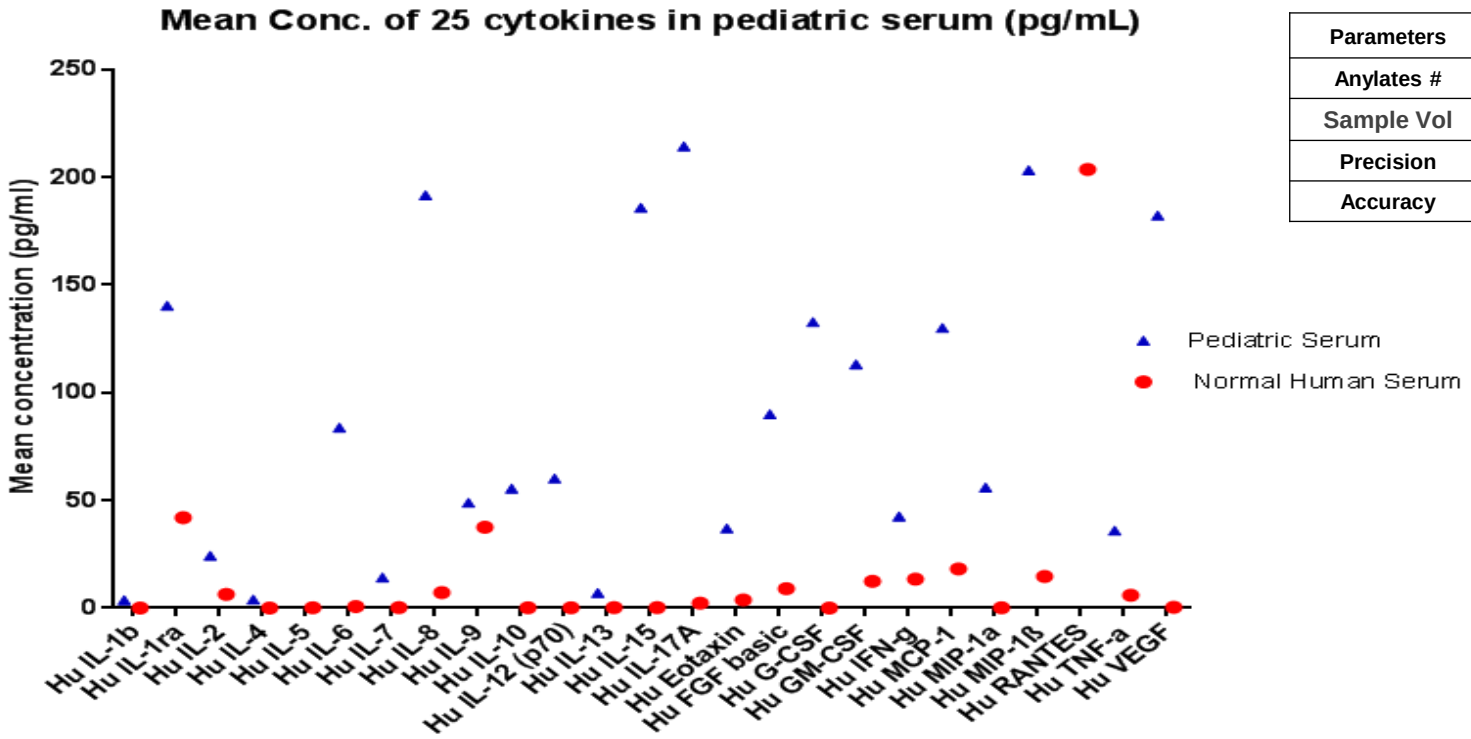
For example, next-gen immunoassays are now well suitable for targeted protein profiling to identify potential biomarkers in neonates



Next-gen immunoassay technologies

- Quanterix (Simoa HD-1)
- Erenna (EMD Millipore)
- Ella Simple-plex (Protein Simple)
- Digital Microfluidics (Baebies)
- Aushon
- Bioplex
- …

Cytokine/Chemokine Levels in Pediatric and Adult Serum Using Bead-based Luminex Multiplex Kits (Bioplex)



Parameters	Luminex
Anylates #	27 plex
Sample Vol	20-30 µL
Precision	<20%CV
Accuracy	±30%RE

Data from Shire's own evaluation

Summary

- Knowledge on potential PD protein biomarkers for neonate patients is very limited in comparison with children and adult populations due to unique challenges in sample availability as well as technical limitations

- New technologies such as Next-gen immunoassays capable of detecting multiple protein biomarkers in miniscule amount of blood samples are now available for us to build up the protein biomarker knowledge base, which is critical for decision making in future clinical trials on neonates

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Pediatric Precision Medicine in Pharma

Thomas Morgan, MD FACMG (Novartis)

Promise & Pitfalls of Next Generation Sequencing in Newborns

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Pediatric Precision Medicine in Pharma

Promise & Pitfalls of Next Generation Sequencing in Newborns

Thomas Morgan, MD FACMG (Novartis)

Applying Regulatory Science to Neonates, EMA workshop

Canary Wharf, London, 12-13 September 2016

NOVARTIS

Next Generation Sequencing of the next generation

Babies being born into big data

- *Over the course of the next few decades, DNA sequencing will lead to each baby's genome being sequenced, and used to shape a lifetime of personalized strategies for disease prevention, detection and treatment.*

- National Institutes of Health Director Francis Collins, *Wall Street Journal*, July 8, 2014.

10 years ago – Classic biochemistry

3 day old full term girl
presents with vomiting of feeds, lethargy, hypothermia and coma

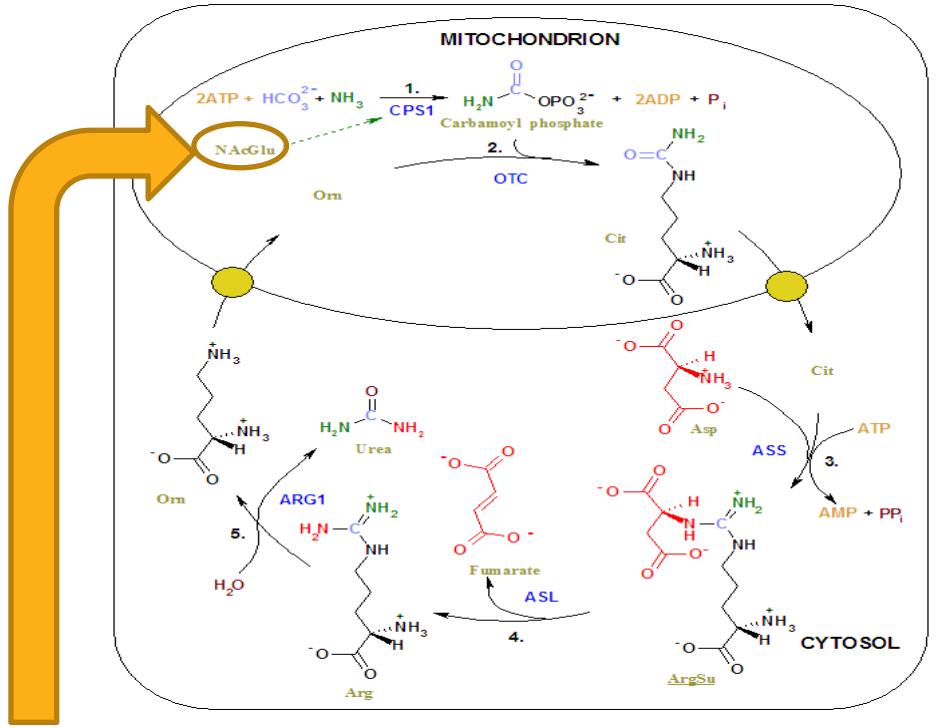
Blood ammonia = **1100**
Protein restriction, ammonia scavengers, hemodialysis

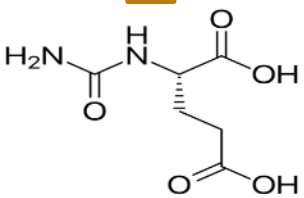
2020 – Precision Medicine?

1-day old full term found to have NAGS homozygous W320X mutation by rapid genome sequencing prior to hospital discharge (not yet ill!)

Blood ammonia **110**
Carglumic acid treatment →
(FDA/EMA approved)

Boris TM Wikipedia Creative Commons





Urea cycle: waste nitrogen from protein goes into urine

Pitfalls of Pediatric Precision Medicine in Pharma

*Right drug to right patient **of right age** at right time*

- Pharmacogenetics (PGx) is the study of variation in drug metabolism in relation to personal genetic variation
- ADME: absorption, distribution, metabolism, excretion
- Problem: drugs often used “off-label” in pediatrics
- Problem: most PGx drug labels based solely on adults
- ***What about “off-label use” of PGx labels in pediatrics?***
- Will genome sequencing of newborns fill the data gap?

ADME “ontogeny”

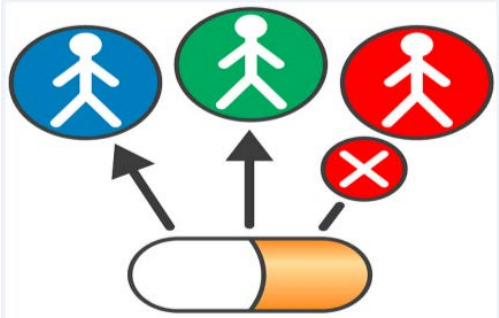
Development of drug metabolism in children

- Drugs aren’t studied in healthy kids (for their safety)
- ADME is a moving target in children
  - LESS or MORE metabolism than adults for dose equivalents
- Particularly in first 1-2 years of life (especially preemies)
- Stomach acid, liver enzymes/bile, kidneys – all different!
- Kids may take different formulations than adults (liquid)

Newborn Precision Medicine - ADME genetics

High degree of analytical difficulty

- ADME gene variants not easily determined
- *CYP2D6* pseudogenes, *CYP2D7* and *CYP2D8,* for example, create confusion when “calling” genetic variants
- Can call ADME variants from whole genome sequence – but methods are not validated via companion diagnostic process for nucleic acid based tests (to go with the drugs)



FDA.gov

Precision Pharmaceuticals in Newborns

Good planning, smart regulation, lots of cooperation needed

- Children, parents, health systems, pediatric professionals, pharmaceutical companies, and governments have stakes
- Special pediatric and maternal-fetal concerns
- Genome sequencing projects in newborns/children must take on the challenge of ADME genotyping before we can even start to fill the knowledge gaps about drug safety
- Smart regulation requires lots of cooperation – it's the joint responsibility of regulators and regulated entities
- Right balance of process and progress is needed

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Precision Medicine for Neonates: Horizon Scanning session

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Research horizon scanning

Personalised **diagnostics**

- *Studies/substudies to reach internationally agreed taxonomy (e.g. BPD)* for well defined clinical phenotypes
- Elements in pre-term/term *groups definition* (beyond age and weight…)
  - *Maternal/foetal health status/ interactions*
  - *Foetal DNA sequencing* in maternal blood
  - *Next Generation Sequencing (NGS) in premature babies*
    - *Diagnostic Biomarkers (validated and putative) relevant to the condition*
    - Baseline sequencing for ontogeny studies

Research horizon scanning

Personalised **response predictive** approach

Response Predictive Biomarkers

- *Prediction with NGS with clear scope and consent: ADME enzymes (-> PK modelling, dose optimization), genomic targets of the drug MOA, genetic of safety response , dynamic genomics as markers as short term surrogates*
- *Neonatal risks from maternal issues*
- *Genomic sampling for future use*

In silico disease models

- *Disentangle developmental vs treatment effects*

Research horizon scanning

Personalised neonatal studies models and simulation

Clinical trial simulation before starting the trial: design choices most influential for the profile of the patients?

Models for transition to Real World Data (RWD) generation

Build in to the models and clinical trial simulations environmental factors such as maternal health/smoking habits/healthcare systems

Long term longitudinal follow-up

registries and observational cohorts, including genetically profiled nests (genomic sampling for future use)

- *Long term clinical outcomes of treatments in neonates*
  - *developmental vs treatment effect*
  - *genomic/molecular changes related to treatment pressure/organs maturation*
- *Public Health impact and cost-effectiveness*

Thank you for your attention

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Further information

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Precision Medicine for Neonates: Horizon Scanning session

Cynthia Powell

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Underlying Principles of Precision Medicine

- Brief overview of NSIGHT projects: Newborn Sequencing In Genomic medicine and public HealTh (NSIGHT) program is to explore, in a limited but deliberate manner, the implications, challenges and opportunities associated with the possible use of genomic sequence information in the newborn period. Funded by NICHD and NHGRI.
  - Sequencing of critically ill newborns (Boston/Baylor; Kansas City/UCSD-Rady
  - Sequencing in “healthy” newborns/public health and genomic newborn screening (Boston/Baylor; UCSF/CAPH; UNC-CH)
- FDA oversight/IDE requirements

Net Results

- Newborn screening for rare diseases
  - RUSP (Recommended Uniform Screening Panel) in U.S., requirements and need for additional data
  - Breakthroughs in treatments for rare diseases
    - Improved outcomes when treatment begun early/pre-symptomatically
    - Even when no treatment in traditional sense, early diagnosis can be helpful in avoidance of diagnostic odyssey, referral for early intervention services, etc.
  - Most neonates with rare diseases are not admitted to NICUs
  - Ability to detect “non-treatable” conditions with genomic sequencing
  - Facilitating technologies – need for high-throughput (next gen targeted panels, microfluidics, expanded MS-MS)
  - Standard public health newborn screening does not require consent and consent required for pilot studies of potential “screenable” and/or “treatable” conditions
    - Need for voluntary/consented supplemental newborn screening – Early Check project
- Future possibilities – prenatal newborn genomic screening through free fetal DNA in maternal blood
- Ethical considerations – secondary (“incidental”) findings, genetic testing in minors, autonomy, right “not to know”

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Principles of Precision Medicine

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Underlying Principles of Precision Medicine

- Phenotypic Precision
  - Validated clinical diagnostic criteria
- Pathogenetic Precision
  - Validated molecular/other pathogenesis
- Pathogenesis Stratification
  - Validated molecular/other biomarkers
- Therapeutic Targeting Based on Pathogenesis
  - In-born errors (CF), oncology (molecular drivers)
- Clinical trial entry based on precise phenotype, stratified by precise etiology
- Precise, measurable outcomes of clinical relevance

Net Results

- Large Effect Sizes
  - Smaller, more informative clinical trials
- More effective real world therapeutics
  - CF G551D as good as it gets
  - Consider surfactant
    - And compare to challenges of addressing current neonatal sources of morbidity and mortality

Voting Slide – Precision Medicine

Considering both impact and feasibility, which of the following projects is your **first** choice?

1. Should genetic / pharmacogenetic studies in neonates be the same as or different to other populations?

2. Should genetic / proteomic studies in neonates be the same as or different to other populations

3. Should the regulatory implications of neonatal genomic/proteomic studies be addressed now or when the field is more mature?

4. What criteria should contribute to quality control of information flow from tests to releasing information to families: which criteria are specific to neonates?

5. “Walk-in Option A” (offered up by audience)

6. None of the above

Voting Slide – Precision Medicine

Considering both impact and feasibility, which of the following projects is your **second** choice?

1. Should genetic / pharmacogenetic studies in neonates be the same as or different to other populations?

2. Should genetic / proteomic studies in neonates be the same as or different to other populations

3. Should the regulatory implications of neonatal genomic/proteomic studies be addressed now or when the field is more mature?

4. What criteria should contribute to quality control of information flow from tests to releasing information to families: which criteria are specific to neonates?

5. “Walk-in Option A” (offered up by audience)

6. None of the above