NEW YORK STATE | Department of Health | Wadsworth Center

Pilot Screening in NY: ScreenPlus

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Thanks to Dr. Melissa Wasserstein for many slides

What is the ScreenPlus Pilot?

A consented population-based ***research**** ***study*** to assess the suitability of specific disorders for public health mandated screening: Includes LTFU and ELSI Studies.

*Research is defined by federal regulations as “a systematic investigation, including development, testing, and evaluation, designed to develop or contribute to generalizable knowledge”

Previous Pilot:

The Lysosomal Storage Disorders: A Pilot Newborn Screen and Examination of the Associated Ethical, Legal and Social Issues

- Live Screening: 2013-2017
- Identified, consented, and prospective program
- Overall consent rate: 73%*

  (*includes days with no recruitment (weekends, recruiter vacations, etc)
- Consent rate when recruiters present: 86%
- Large number of later onset phenotypes detected

Take Home Lessons from NY Pilot NBS for LSDs

- NBS for LSDs remains challenging
  - It is more likely to detect later onset phenotypes
  - There is room for improvement with respect to accuracy of the screening assays (pseudodeficiency, heterozygotes, false positives, *phenotype differentiation?*)
    - Use of multienzyme approach for "cutoffs"
    - 2nd and even 3rd tier testing
    - CLIR tools (? For LSDs?): we will have an 11-plex enzyme assay
- Organized, long term data capture is possible
- Large scale opt in consenting is possible
- Most parents want to participate in pilot NBS
- Many parents seem eager to "be heard" in the discussion about ethical aspects of NBS
- Big challenge is sorting and pulling of specimens for the pilot
- Treatment is available, if not detected now, then when...?

The infrastructure works!!!

Overarching Goals of ScreenPlus

- Evaluate the analytic and clinical validity of the screening assays, determine cutoff values for referral, and define disease “incidence” (caveat, possible disease incidence) – can we make these screens work.

- Determine the impact of NBS on phenotype/outcome through longitudinal follow up of true positive infants.

- Examine the ethical, legal, and social issues (ELSI) associated with screening newborns for complex disorders: Is this screening acceptable to the “general public”?

Criteria to be on ScreenPlus Panel

- A DBS screening assay that can be multiplexed, and that is high-throughput, reasonably priced, and has had positive baseline validation studies;
- Significant morbidity or mortality if untreated;
- A pediatric phenotype; and
- An FDA approved treatment(s), or treatment(s) currently in clinical trial.

Initial Panel (enzyme assay and marker assay)	
ASMD	Acid sphingomyelinase deficiency
CLN2	Ceroid lipofuscinosis type 2
CTX (marker)	Cerebrotendonous xanthomatosis
Gaucher	Gaucher disease
GM1	GM1 Gangliosidosis
Fabry	Fabry disease
LAL-D	Lysosomal acid lipase deficiency
MLD (marker)	Metachromatic leukodystrophy
MPS II	Mucopolysaccharidosis type II/ Hunter
MPS IIIB	Mucopolysaccharidosis type IIIb/ Sanfilippo IIIb
MPS IVA	Mucopolysaccharidosis type IVa/Morquio IVa
MPS VI	Mucopolysaccharidosis type VI/ Maroteaux Lamy
MPS VII	Mucopolysaccharidosis type VII/ Sly
NPC (marker)	Niemann Pick C

Using ScreenPlus to Enhance the Accuracy of Screening

- multienzyme, biomarkers and DNA testing on the DBS enhance accuracy?
  - Reduce false positives?
  - Predict phenotypic severity?
- How do we determine referral cutoffs using 3 tiered approach?

Disorder	First Tier	Second Tier (Mayo)	Third Tier
ASMD	ASM	Lyso SM	DNA
CLN2	TPP1	-	DNA
CTX	Bile tetrol glucoronide	-	DNA
Fabry	GLA	Lyso Gb3	DNA
Gaucher	GBA	Lyso Gb1	DNA
GM1	GM1		DNA
LALD	LAL	-	DNA
MLD	Sulfatides	Enzyme	DNA
MPS II	I2S	DBS GAG	DNA
MPS IIIb	NAGLU	DBS GAG	DNA
MPS IVa	GALNS	DBS GAG	DNA
MPS VI	ARSB	DBS GAG	DNA
MPS VII	GUSB	DBS GAG	DNA
NPC	Bile Acid B	COT	DNA

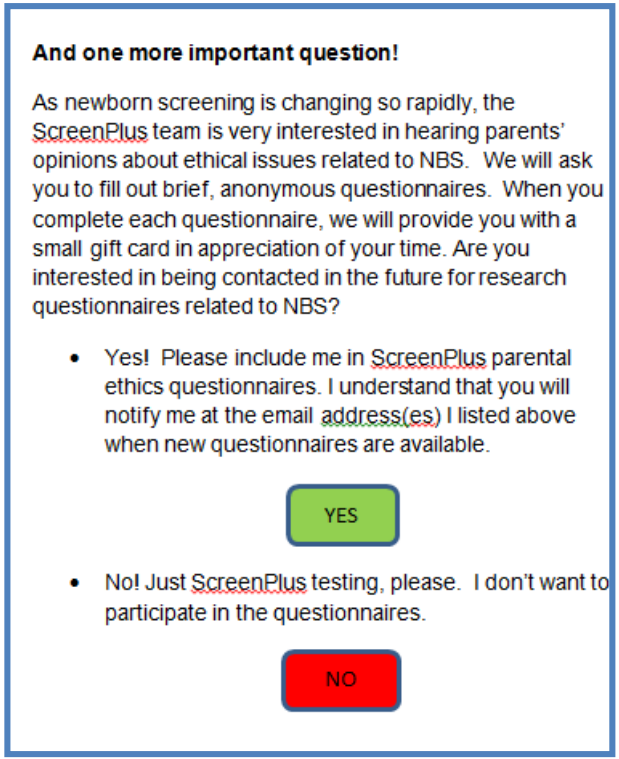
Long-Term Follow-Up

We will establish standardized follow up protocols and data collection forms for each disorder

- Multiple follow up sites: Need algorithms for testing, frequency of visits, and guidelines for treatment referral
- We have worked with NBSTRN in first round and created data collection forms for LSDs with help from the Longitudinal Pediatric Data Resource team

ELSI Surveys

- It is critical that parents are involved in the process of evaluating the potential benefits and harms of expanding NBS panels
- At time of e-consent, we will ask all parents if they're interested in participating in surveys
  - Survey #1: Satisfaction with IC process
- We will have access to thousands of parents who are willing to opine about NBS
- We will include qualitative interviews
  - QI #1: Experience of parents of true positive/uncertain status babies



Laboratory and Program Challenges

Clinical Lab Evaluation Program: Method Validation Requirements

Basic requirements:

- Practitioner and patient educational materials
- Specimen collection and handling
- Description of assay
- Complete and detailed procedures, algorithms and flowcharts needed to perform the assay
- Equipment, reagents, standards, calibrators, interferences and limitations
- QA/QC requirements
- Requisition and reporting requirements
- references

CLEP Method Validation Requirements (continued)

Validation summary, protocol and representative data:

- Analyte and specimen matrix stability
- Specimen transport conditions
- Storage time and temperature
- Precision and accuracy studies -challenging
- Reportable range
- Limits of detection or quantitation
- Sensitivity and specificity

After validation

- Run anonymized specimens
- Compare data to published data
- Set preliminary cutoffs, ideally would test know positives from saved residual newborn screen samples
  - Comparison of population mean/median/stdev (measure of bias)
  - Compare results of any positive controls
  - Enzymes, if using comparable methods, can use percent of median or mean for cutoffs
  - If marker assay and concentrations are near “0”, than bias needs to be measured with other controls in order to estimate cutoffs
- Working with limited data and positive controls: start off with conservative cutoffs based on prior work

Unique Issues with Pilot Screening

- Only testing a subset of the samples that come in: will be provided a list of newborns whose parents consented to testing
- Do not want to delay reporting of routine screen results
- List will “unmail” the specimens and add Pilot test codes for data
- Test requires three punches, may need to request repeats on samples that had marginal amount of blood
- Delayed testing and delayed results: we set up LIMs so routine panel can be reported earlier, followed by an amended report.
- Monitoring and resetting cutoffs will be based on data from second tier biochemical and molecular results and follow-up work

- Less than perfect screening (it’s a pilot), testing 14 disorders: offers us a chance to detect newborns with disease

- Food for thought: is it better to run many less than perfect tests, seting up for few false positives, to improve the chances of detecting someone with a disease that can be treated?

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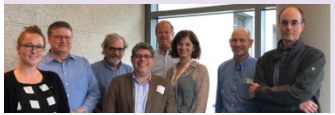

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