From Newborn Screening to Newborn Genome Sequencing: Combining the Power of WGS with Cord Blood Storage Through the Generation™ Program

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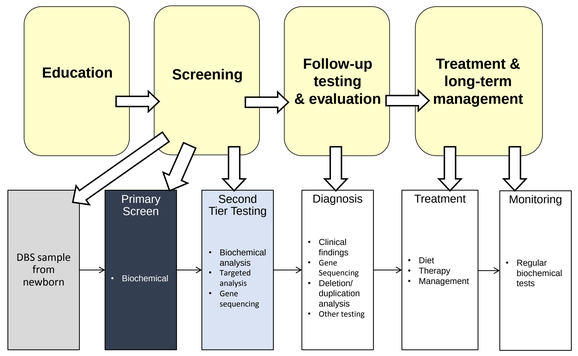
Newborn Screening (NBS) in the US

- ~4M births a year
- Public health program, mandated in all 50 states
- Uniform screening panel identifies a minimum recommended list (currently 34 core conditions + 26 secondary conditions)
    - Procedure for nominating and adding conditions
        - Three conditions have been added since the initial panel was identified (CCHD, Pompe, SCID)
        - States can add or remove conditions (each state has its own laws), most currently considering certain LSDs
- Dried blood spot biochemical testing used for most tests
    - Point of care testing used for some tests (hearing loss, CCHD)
    - Molecular testing used for some tests and secondary tests (SCID, CF)

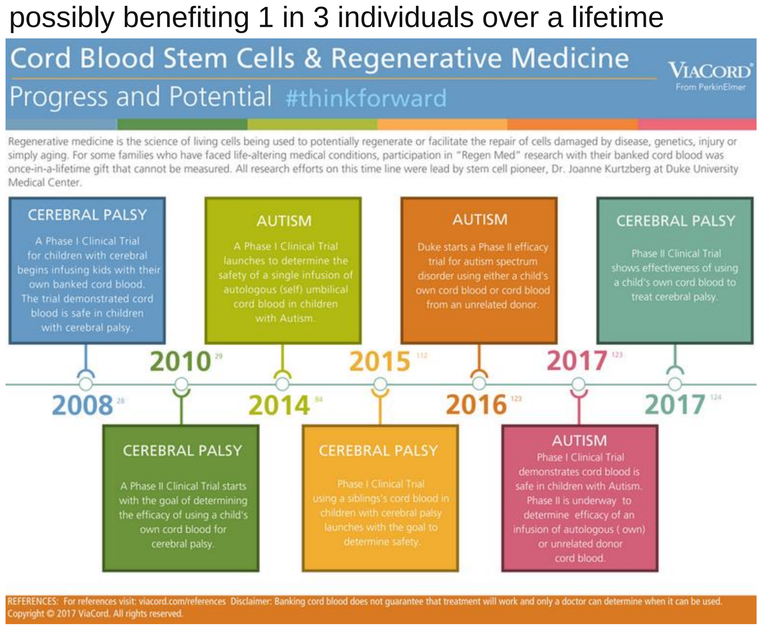
Benefits
- Identification
- Early intervention
- Reduced morbidity & mortality
- Family Planning

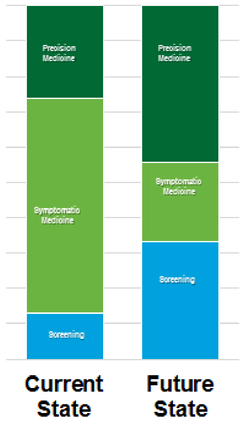


Steps involved in the process of NBS

Cord Blood and Cord Tissue Banking

- Cord blood and cord tissue contain a variety of stem cells
- Stem cells can be extracted and cryopreserved
- Cord blood stem cells currently used in treatment of almost 80 disorders, including:
    - Cancers
    - Bone marrow failure syndromes
    - Blood disorders
    - Metabolic disorders
    - Immunodeficiencies
- Research is progressing for using cord blood stem cells for regenerative medicine – regenerating or facilitating the repair of cells damaged by disease, genetics, injury, or aging, possibly benefiting 1 in 3 individuals over a lifetime

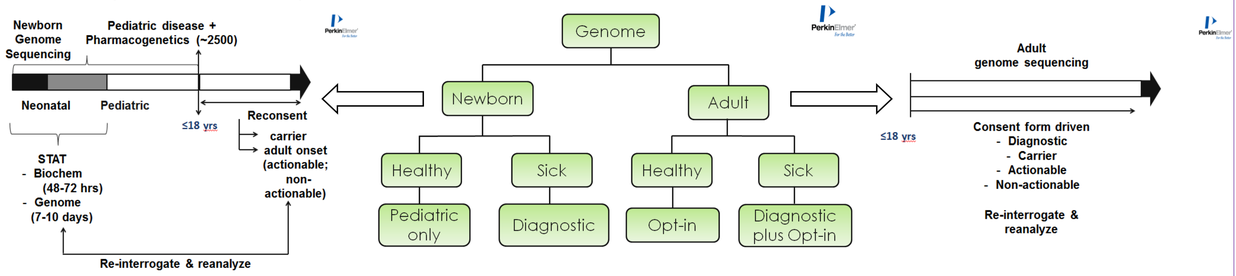




Currently, the majority of medicine is practiced after symptoms have already begun. Through the use of programs such as NBS, cord blood banking, and WGS of newborns and healthy individuals, the proportion of symptomatic medicine is expected to decrease while that of preventative and precision medicine to increase.

Generation™ Whole Genome Sequencing Program

- Optimized WGS on stored cord blood and dried blood spot (DBS) cards
- Bioinformatic analysis using Edico Genome® Dragen™ platform and an internal variant interpretation platform, ODIN
- ~2500 curated genes are analyzed for infant and pediatric onset conditions
- Report generated for pathogenic and likely pathogenic variants identified in these genes
- Adult onset disease genes are not analyzed –sequence data for these genes is bioinformatically partitioned from primary analysis directly to archive storage
- When the child turns 18, he or she can consent to the return of the rest of the WGS results, including adult-onset medically actionable and adult-onset medically non-actionable diseases
- Other options for reanalysis as healthy WGS in the future as new disease genes are discovered, and as diagnostic WGS in the event that the child becomes ill with a suspected genetic disease
- Parents may also order healthy WGS on themselves and opt-in to receiving pharmacogenetic variants, carrier status, and medical actionable and non-actionable conditions



How Generation™ newborn healthy WGS differs from diagnostic WGS in a newborn, and from adult WGS.
In WGS for healthy newborns, only variants in genes causing infant and pediatric onset conditions are analyzed, and pathogenic and likely pathogenic variants are reported. In a diagnostic WGS for a newborn, variants of uncertain significance will also be reported, and if potentially causative variants are not identified in the infant and pediatric onset genes, the variants in the rest of the genes can be analyzed. Parents can also opt in to have pharmacogenetic variants included in the analysis and report.
In WGS in adults, in addition to any variants related to any phenotype the individual may have, the adult may opt in to have pharmacogenetic variants, carrier status, and pathogenic and likely pathogenic variants for actionable and non-actionable conditions reported.

Preliminary Findings

- Originally offered testing to families that had already banked cord blood, therefore had older infants or children, not newborns
- Initial requests have been mainly for diagnostic exomes on children with banked cord blood – autism, developmental delay, speech delay, sibling with autism, etc.
- Parents are requesting WGS as well, both healthy and diagnostic – hypogammaglobulinemia, common variable immune deficiency, porphyria, elevated urine copper, mast cell activation syndrome, fatigue, photosensitivity, anxiety, fatigue
- No definitive diagnostic findings in children or adults; some variants of unknown significance or a single pathogenic variant in a recessive disease
- Adult with homozygous *AMPD1* common pathogenic variant as incidental finding in diagnostic WGS (myopathy due to AMPD1 deficiency, reduced penetrance)
- Adult onset condition VOUS in *PKP2* (arrhythmogenic right ventricular dysplasia 9, autosomal dominant)
- Most adults carriers of one to two conditions and have one to two pharmacogenetic variants
- Performed WGS on both cord blood sample and saliva sample from a 2.5 year old – no differences found
- Some adults and even some ordering physicians expressed surprise that the report did not include "hundreds of variants" indicating increased/decreased risk or likelihood of disease, or results of non-health-related traits often found on "recreational" genomics reports common in direct-to-consumer genetic testing

Conclusions

- When offered to families who already had cord blood banked, those with affected children were eager to order testing, even though it was marketed as "healthy" WGS testing for newborns
- Some parents order testing on themselves before ordering testing on their children, possibly as a way to "warn" or "prepare" themselves for any unexpected results they may receive in their child before deciding whether or not to test their child, or to diagnose themselves before deciding whether or not to test their child
- Education is needed to inform both physicians and the general public of the difference between a health related WGS report and a "recreational" genomics report or risk allele report