

# Molecular-Based Newborn Screening for Cystinosis and Spinal Muscular Atrophy (SMA) in Germany

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## Background

Population-based newborn screening (NBS) is an important public health program that has vastly improved the course of several diseases through early detection. Current NBS methods, which employ tandem mass-spectrometric analysis of newborn dried blood spots, cannot detect many potentially treatable genetic conditions. At the same time, molecular-based NBS is increasingly feasible due to the following reasons: DNA can be extracted from a dried blood spot, next generation sequencing has become economical, and molecular diagnostics have greater reliability and increased validity as genetic databases become more refined and comprehensive.

This NBS pilot study employed the existing German NBS framework to incorporate first tier, high-throughput **molecular genetic screening for cystinosis and SMA** in newborns.

## Materials & Methods:

- This prospective pilot study was performed within the German NBS framework. (BLAEK, Ethic permit No.16125)
- Parents received an information sheet (Supplement) clarifying the screening process and objectives, the potential risks and benefits, possible results of non-participation, the molecular nature of the screening, and the validity of the test results.
  - DNA, extracted from dried blood cards collected as part of the regular NBS program, was screened for cystinosis and spinal muscular atrophy (SMA).
  - First tier multiplex PCR was employed for both diseases.
  - The cystinosis screening employed assays for the three most common CTNS mutations (57kB-Deletion, 357delGATC, 1261insG), covering 75% of German patients.
  - In case of heterozygosity for one of these mutations, samples were screened by next generation sequencing (NGS) for 101 CTNS mutations. With this approach, a sensitivity of 98.5% was calculated.
  - For SMA, PCR detected homozygous deletions of exon 7 of the SMN1 gene.
  - Parents were informed immediately of a positive result and transferred to a center.

## Results

**Cystinosis Screening:** 01/15/ 2018 – 08/31/2019      n = 304.144 newborns  
n = 2 homozygeous 57-kb-Mutation  
n = 1 homozygeous 57-kb-Mutation\*

\* Initially, parents refused the newborn screening for cystinosis. At the age of 7 months, the infant demonstrated severe electrolyte disturbance. The newborn screening test for cystinosis was given and the infant was tested positive.

After the diagnosis was confirmed with cystine level in white blood cells, oral therapy was started with cysteamine. The prevalence was 1 /100.000.

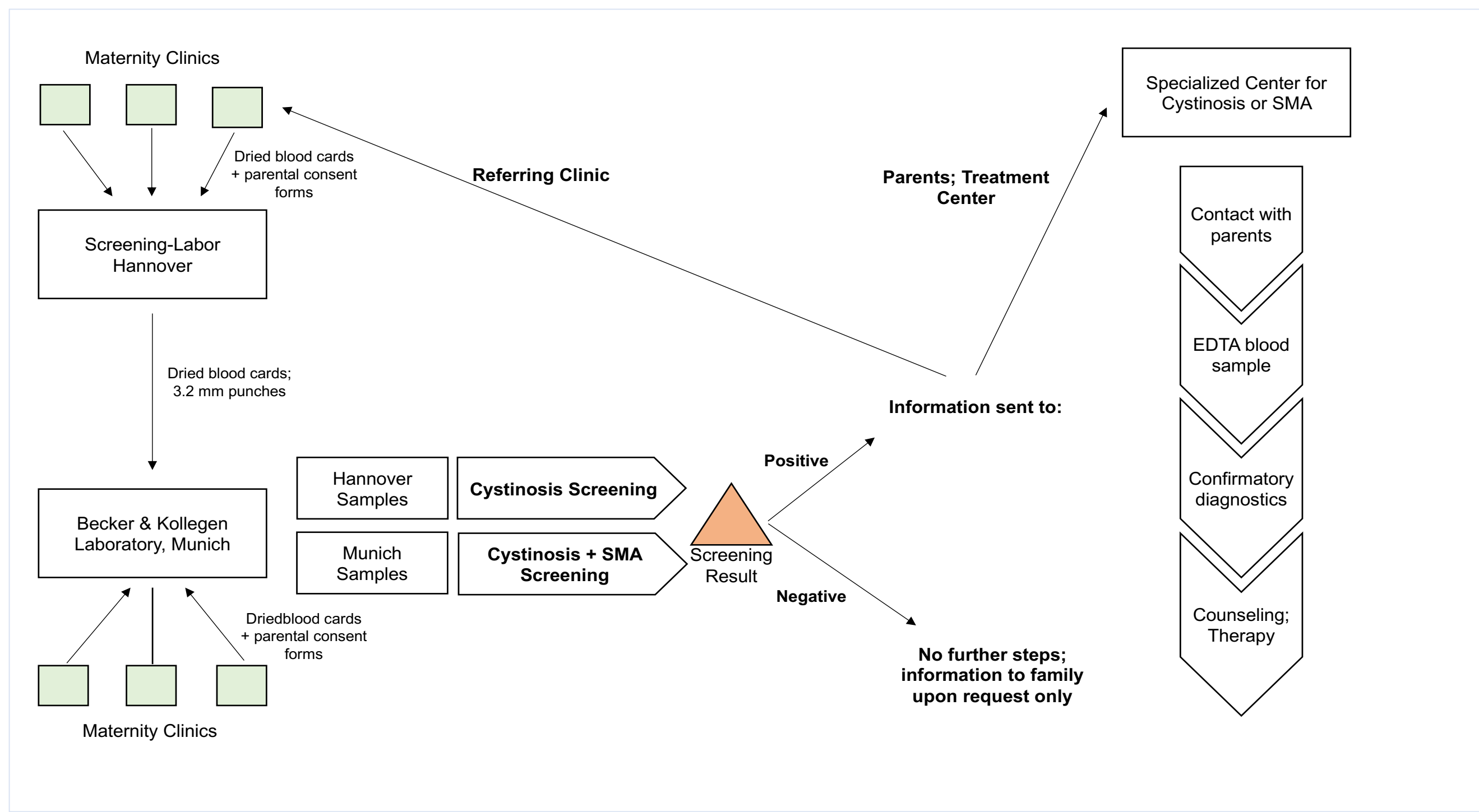
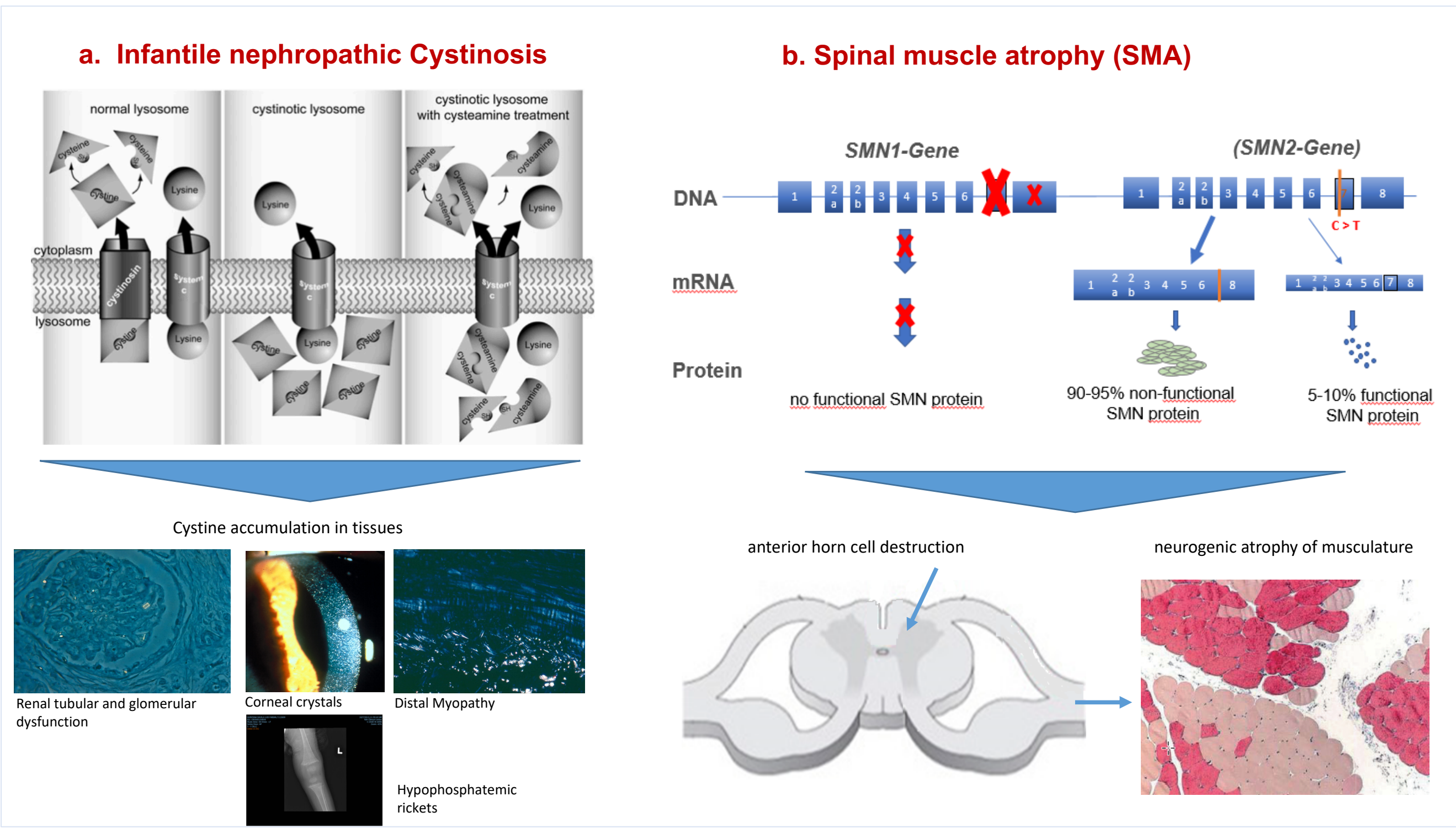
**SMA-Screening:** 01/15/ 2018 – 08/31/2019      n = 200.901 newborns  
n = 29 positive results for SMA

Immediate presentation in a neuropediatric center. Start of therapy with Nursinersen® or with close clinical surveillance (Prevalence 1/6.928).

- No false positive or false negatives have been detected so far.
- Screening, communication of findings to parents, and confirmation of diagnosis were accomplished in a multi-disciplinary setting, on average, by day 15 of life.
- This program was well accepted by hospitals, physicians, and parents.

## Conclusion

**This pilot study demonstrates the efficacy of a molecular-based neonatal screening program for cystinosis using an existing national screening framework.**



	Cystinosis	heterozygeous 57 kb	c.18_21del GACT (=357delGACT)	c.926dupG (=1261InsG)	homozygeous
15.01.2018 - 31.08.2019	301,144	676	83	58	57 kb: 3

	SMA	2 copies	3 copies	4 copies	unknown
15.01.2018- 31.05.2019	200,901	11	5	12	n=1