INTRODUCTION

- X-linked adrenoleukodystrophy (X-ALD) is a metabolic disorder with an estimated incidence of 1:17,000.
- It is characterized by progressive deterioration of the adrenal glands, spinal cord, white matter of the nervous system.
- Phenotypic features range from adrenocortical insufficiency (Addison disease), to a progressive adult on-set paraparesis with adrenal gland dysfunction (adrenomyeloneuropathy, AMN), to the most severe and fatal cerebral form of X-ALD.
- ABCD1, encoding the adrenoleukodystrophy protein (ALDP), is the only gene known to cause X-ALD.
- X-ALD is inherited in an X-linked manner with males more severely affected than females. About 80% of female carriers will develop neurological symptoms, usually in the fifth decade.
- Newborn screening (NBS) is a public health service designed to identify individuals who may be at an increased risk of a variety of severe conditions at birth.
- It allows doctors to start treatment before some of the harmful effects happen.
- NBS is not a diagnostic test. It identifies individuals who may have the condition so that confirmatory follow-up testing can be offered to determine if the condition is truly present.

RESULTS

- PKIG received and tested 206 dried blood spot (DBS) samples, including 94 males and 112 females, from February 2017 through February 2018.
- A pathogenic/likely pathogenic (P/LP) variant or a variant of uncertain significance (VOUS) was detected in approximately 66.5% (64M+73F) of samples while approximately 33.5% (30M+39F) of cases yielded a negative result (Fig. 1).
- The number of cases with a P/LP variant or a VUS was 56 (27.2%) and 81 (39.3%), respectively.
- Among 19 males with parental testing, one pathogenic and one VOUS ABCD1 variant occurred de novo; and three pathogenic variants were maternally inherited.
- In 21 female newborns with parental testing, three pathogenic variants were de novo, two were inherited maternally and one was inherited from a reportedly unaffected father (Table 1).
- Three ABCD1 VOUS carried by females were inherited from their reportedly asymptomatic fathers while four females inherited ABCD1 VOUS from their mothers (Table 1).
- Two males with a ABCD1 pathogenic variants were mosaic (Fig. 2) and one with potential deletion of exons 8-10 (Fig. 3).

CONCLUSION

- Second-tier confirmatory NBS testing of ABCD1 is essential to identify and ascertain affected individuals with positive VLCFA accumulation.
- The molecular confirmatory data will be helpful in assessing the NBS biochemical cut-off values for calling positive result.
- Future in depth study of biochemical and molecular data will also benefit accurate interpretation of ABCD1 variants as well as genotype-phenotype correlation.

REFERENCES
2. Adrenoleukodystrophy Database (www.x-ald.nl)