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"Genetic testing in rare forms of primary adrenal insufficiency"

Key points for ERN:

- Primary adrenal insufficiency (PAI) is a potentially life-threatening condition due to glucocorticoid insufficiency, often with mineralocorticoid insufficiency
- Presentation can be very variable, such as with severe salt-losing crisis, or more gradually with non-specific features such as low energy, and slow recovery from common viral infections
- The diagnosis is often not thought about as it is rare, but skin hyperpigmentation and high ACTH are good clues
- Education about steroid replacement is crucial; clinical nurse specialists can play an important role in supporting and teaching families

- Genetic forms of PAI are common in childhood (around 30 different ones), whereas in adults PAI usually results from autoimmune origins (Addison disease) or other causes with a less obvious genetic basis
- Considering all forms of childhood PAI (including congenital adrenal hyperplasia and metabolic causes), a genetic diagnosis can be made in around 90% of children
- Many distinct genetic causes fall under an "umbrella" term of "PAI", but reaching a specific condition can be important for understanding the natural history of a condition, modifying treatments, looking for associated features, understanding inheritance patterns, and identifying and treating other "at risk" family members before they get unwell.

- Genetic testing for childhood PAI has been helped by next generation sequencing (NGS), which allows many genes to be analysed at once
- This means genetic analysis can be done quickly and more cost-efficiently
- Research studies around the world have shown the range of genetic conditions; "hotspots" and founder effects are important for rare conditions
- In some countries, clinical genetic testing is available using "panels" of key genes, or whole exome sequencing

- Future challenges include discovering more novel genetic causes of PAI, and using genetic testing in the newborn period to screen for PAI before the onset of clinical features
- As these genetic conditions are individually rare, there are only a limited number of support groups currently available
- Genetic and genomic analysis is important to improve care for children and their families, but access to services in variable in different countries and different centres
- The initiatives led by ENDO-ERN related to genomics will be an important way forward; research studies have shown the importance of PAI genetic testing and this needs to be considered at the clinical interface.