**Box S1. Parents’ experiences: the journey of WES testing.**

Reflecting back to our son’s first few months of life in NICU, to when the process of genetic testing began, the hardest and most stressful part was waiting for results. We hoped something would be found that would explain our son’s complex medical conditions, many that were of “unknown cause”. We prayed for a diagnosis that had a cure; and we dreaded a diagnosis without a cure. Test after test came back negative. We understood that each test was a process of elimination and were thankful that the results were negative. When whole-exome sequence testing started, some genetic variants were found, but they did not provide a reason for our son’s condition.

Before our son’s second birthday we were informed that medically there was nothing more that could be done that would improve his life. In the following weeks we were having discussions with the Paediatric Advanced Care Services since our son was deemed palliative. Physical, emotional, and mental exhaustion was really beginning to set in. We inquired as to whether genetics would consider further testing as we still had hope that a diagnosis could be found. Not a cure, but at least something that would explain the cause of our son’s conditions. We were told that any further testing would be research based.

In the fall of 2015 our son’s whole-exome sequencing data was reanalyzed, and in less than six months, we were given the diagnosis of PRUNE. It was further explained to us that there were only a handful of confirmed cases worldwide, and that the effects of PRUNE mutations were still being researched. So unfortunately there may not be answers to some of our questions.

Since the diagnosis of PRUNE, along with the forecasting of the probable course of our son’s complex conditions, we have come to a sense of reconciliation. We have always accepted that our son may not be able to experience the physical aspects of life that we take for granted, and that it is only a matter of time that his medical conditions overcome his body. We’ve come to terms that most likely there will not be any treatment options available to him during his lifetime. But at least we know a cause and have a diagnosis. Our biggest resolution is that his complex medical journey thus far has not been taken for granted, and that somehow he validated the need for whole-exome sequence testing when it comes to complex medical conditions of ‘unknown cause’.

Our son’s medical journey has been one of anxiety, stress and exhaustion. It challenged aspects of our family, friendships, relationships, beliefs, and our confidence as parents. But through it all, the greatest aid to this journey has been the support of and access to medical teams and care of our health care team. We will always be grateful for this.