**Title**: A Data-Driven Analysis of Health Profile Shifts in Down Syndrome Regression Disorder

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**Introduction**: Down syndrome regression disorder (DSRD) is a rare, poorly understood condition associated with a sudden loss of previously learned abilities in adolescents and young adults with Down syndrome (DS)1–3. DSRD represents with a rapid decline in domains such as daily living activities, behavioral regulation, cognition, language, social skills and movement3,4. It also manifests with psychiatric symptoms such as depression, psychosis, or catatonia4. DSRD has a devastating effect on patients and their families and negatively impacts multiple aspects of the patient’s well-being and quality of life4. Early diagnosis of patients will enable timely access to therapeutics and intervention, which can improve patients’ outcome. Identification of early signs of regression will provide critical information for families, physicians and policy makers and can assist in developing new approaches in preventative care and intervention. In this study, we compared the electronic health records (EHRs) of patients the year before DSRD diagnosis with the EHRs from the year of diagnosis to characterize the potential changes in the health profile of patients.

**Method**: We leveraged the EHRs from over 6 million patients served by Atrium Health, which is the clinical entity of the Southeast Region of Advocate Health, the third-largest nonprofit integrated health system in the nation. We mined the EHRs to identify all patients with DS. There is no specific diagnostic code in EHRs for DSRD and therefore, we included patients with confirmed diagnosis of neurocognitive decline in this analysis. We investigated the EHRs of patients during the year of DSRD diagnosis and the year before and examined the prevalence of diagnosis and the number of unique codes within different health categories.

**Results**: We identified 5,549 DS patients including 2,885 (52%) males and 2,664 (48%) females. We identified all patients with a code for neurocognitive decline and examine the records to detect patients with confirmed diagnosis for DSRD. 12 patients were identified, among them 8 were female and 4 were male. 66.7 of patients self-identified as White and 16.7% as non-White, others declined to respond. We observed that the number of visits and number of unique codes recorded in the EHRs increased around the time of diagnosis. For example, patients received an average of 40.8 unique codes in the year of DSRD diagnosis, compared to 29.7 codes they received the year before. Percentage of patients with endocrine problems increased to 82% from 36.4% the year before. The number of unique codes within this category also increased to 33 compared to 8. The prevalence of circulatory, respiratory issues, musculoskeletal problems in the year of DSRD diagnosis was twice higher than the year before. Number of unique codes within different categories also increased significantly (between 2-5 times).

**Discussion:** Patients with DSRD are diagnosed with a wide range of medical conditions, around the time of experiencing regression. The variety of diagnostic categories indicates a significant increase in the complexity of health problems in DSRD patients. The significant increase in the number of encounters related to different health categories, shows that patients experience severe symptoms and a high burden of disease. Therefore, sudden change in frequency of encounter with medical system could be a potential early sign of regression in patients.

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