Title: Advancing clinical validity curation and disease naming in hereditary cancer: A comprehensive recuration of breast, ovarian, colon cancer and polyposis disease genes

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Abstract: GUARDIAN (Genomic Uniform-screening Against Rare Disease in All Newborns) seeks to evaluate the implementation and impact of expanded genomic newborn screening (gNBS) at six New York City hospitals.

Over 28 months, 15,000/20,478 (73.2%) parents approached postnatally enrolled. NBS dried blood spots were used for gNBS. All enrollees were tested for up to 321 treatable Group 1 conditions and could opt in to 144 Group 2 neurodevelopmental conditions (gene list expanded from 237 to 455 in March 2024). The majority (92.6%) selected both groups.

Among parents who enrolled their first eligible baby, 87% enrolled their second, suggesting study comprehension and satisfaction. Of parents who declined for their first baby, 35% enrolled the next.

Genetic counselors returned 475 (3.2%) positive screens: 420 (2.8%) Group 1 and 55 (0.4%) Group 2. Confirmatory testing revealed 64 (13.5%) false positives. Notable results included G6PD (n=302), long QT syndrome (LQTS; n=18), SCN1A (n=17; ten inherited with no known family seizure history), Wilson disease (n=10), Rett syndrome (n=4), Fabry disease (n=3), severe combined immunodeficiency (n=2; one received a bone marrow transplant), and achondroplasia/hypochondroplasia (n=2). Babies with LQTS are avoiding contraindicated medications; three began recommended medications, and one mother was diagnosed and initiated treatment. Ten Group 2 babies are symptomatic and receiving neurodevelopmental care and interventions. Diagnoses have motivated some families to utilize IVF and embryo screening for subsequent pregnancies.

Outcomes are assessed longitudinally via a post-results survey, annual health assessment, medical chart review, and interview. Approximately 30% of all families completed surveys with the highest response by Group 2 positives (~50%). The Decision Regret Scale (DRS) revealed low regret for enrollment; the Feelings About genomiC Testing Results (FACToR) Scale showed low to moderate impact of results. Those with positive results reported more regret (DRS) and greater impact (FACToR) than negatives, and Group 2 positives more than Group 1. A notable decrease in Group 2 scores at 12 months on both scales suggests adjustment to the diagnosis and benefit of onboarding to care.

Results indicate low regret and high appreciation for participation both short- and longer-term, including in families receiving difficult diagnoses. Follow-up shows significant, sometimes life-saving impact on infant and family medical management.