Methods: A retrospective chart review was conducted for insurance-authorized, completed pediatric ES where initial requests were reviewed by Stanford’s Genetic Testing Optimization Service (GTOS) between November 2018-December 2019. Regression analysis was used to determine the association between the geocoded median household income and three different time point intervals defined as “Time to test”, “Insurance decision” and “Scheduling/consent”.

Results: Of the 281 charts reviewed, 115 cases were included in the final cohort. The average time from provider pre-authorization request to sample collection took 104.4 days, and income was negatively correlated with the length of the insurance decision interval.

Conclusion: Pediatric patients undergo a lengthy, uncertain process when attempting to obtain ES, some of which is associated with income. More research and clinician interventions are required to clarify specific socioeconomic factors that influence the ability to obtain timely ES and develop optimal protocols.

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Genetics professionals’ perspectives on the reporting of Variants of Uncertain Significance (VUS): Should they always be reported?

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Introduction: Variants of uncertain significance (VUS) are common. With increasing use of multi-gene panels (MGP), the numbers of VUS grow. Not all VUS have the same degree of uncertainty, presenting challenges to non-genetics healthcare providers (HCPs), patients and families. We report the results of a survey assessing attitudes of genetics professionals on the return of VUS results from MGP, emphasizing cancer genetics professionals in academic settings.

Methods: We designed a survey regarding VUS in MGP and exome sequencing (ES); this analysis specifically focused on responses in the context of VUS in MGP. The survey was sent to ASHG and NSGC members to query those having experience with MGP. 2711 confirmed receipt. Initial analysis: 378 respondents (14%), 253 completed the survey (9%); 66% genetic counselors, 21% clinical geneticists, among others; 60% academic, 31% in a private clinical or commercial laboratory setting. 40% work primarily in cancer genetics, 13% in pediatric genetics, 11% adult genetics, skewing the respondents towards those who assess VUS for dominant/incompletely penetrant conditions.

Results: Overall, 47% (total n=167) agree that VUS can be useful for patient care with 30% in disagreement. In the last year, most respondents (75%) received a VUS result they considered clinically significant (prompted family segregation studies, was in trans with P/LP variant in an autosomal recessive condition, etc.), with 67% receiving <10 in the last year. The most frequent concerns for the return of VUS were confusion for the patient (80%) and HCP (74%), and anxiety/stress for the patient/patient’s family (70%). The majority (73%) indicate the primary challenge in returning VUS is that HCPs do not have the time or expertise to explain VUS results. A plurality (40%) placed primary responsibility with the clinical lab for initiating VUS re-evaluation. If initiated in the lab, 23% preferred a cadence of at least every 12 months, or as the VUS reappears during the analysis of other MGPs (23%). Whereas 21% think clinicians should initiate, triggered by changes in a patient’s clinical status. Almost half (46%) think that patient/family preferences should be considered for reporting VUS and a slight majority (51%) agree that the patient/family should have the ability to opt-out of receiving VUS results entirely (32% disagree).

Conclusion: While VUS can be useful in specific circumstances, these data suggest that they present challenges in genetic testing for both patients and HCPs, with the potential to induce patient anxiety/stress. These results indicate support for providing the opportunity to opt-out of VUS return for MGP to patients, in the interest of patient autonomy, and to providers to reduce practice burden. The utility of VUS likely correlates with clinical context (eg, cancer, rare disease, recessively versus dominantly inherited disorders, carrier screening etc.). The clinical impact of VUS on patients and families warrants further investigation.

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Applying the clinician-reported genetic testing utility InDEx (C-GUIDE) to genome sequencing

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Introduction: Genome sequencing (GS) technology currently outperforms other testing modalities for establishing a genetic diagnosis in patients with rare diseases, but access remains limited while payors seek evidence demonstrating appropriate indications, utility, and value to justify the expense. The previously published Clinician-reported Genetic testing Utility InDEx (C-GUIDE) was developed to capture the informational value of genetic testing from a clinician’s perspective and was validated in a cohort of patients who received microarray, single-gene, or multi-gene panels, but had not yet been studied in the context of GS. We aimed to assess the construct validity of C-GUIDE in two US-based clinical genetics centers serving pediatric and adult patients.

Methods: One genetic counselor at the HudsonAlpha Institute for Biotechnology (Huntsville, AL) and one medical geneticist at Children’s of Alabama (Birmingham, AL) completed C-GUIDE ratings for patients who had GS as part of a diagnostic workup and who received positive or negative results for primary, secondary, and/or pharmacogenetic findings. All GS was performed at the HudsonAlpha Clinical Services Laboratory. To achieve a balance of responses across result type (ie, diagnostic, partially diagnostic, potentially diagnostic, non-diagnostic), a stratified recruitment approach was used. The C-GUIDE (Version 1.1, previously published) was completed for each case through an online REDCap link and included questions about the case descriptors, primary variants (PV), secondary variants (SV), pharmacogenetic variants (PGx), a global rating of utility (ie, the utility of all PV, SV, and PGs per case), and rater feedback. For each case, total and global C-GUIDE scores were calculated for each result disclosed. Case and test characteristics were summarized with descriptive statistics, and construct validity was assessed using a generalized estimating equation to determine the association between C-GUIDE scores and global item scores along with other potentially explanatory variables.
Results: A total of 67 pediatric and 36 adult cases were rated (mean age 19.9 years, SD = 21.8), with an almost even male/female split. GS indications included neurological phenotypes (70.9%) and results were diagnostic or partially diagnostic in 28.2%, potentially diagnostic in 36.9% and non-diagnostic in 35%. Secondary findings (including carrier status) were reported in 92.2% of cases and pharmacogenetic findings in 95.1%.

For PV, C-GUIDE total scores ranged from -1 to 26; the mean score was 6.2 (SD = 7.1). For PV+SV, the total score ranged from -1 to 35; mean 11.1 (SD = 7.9). For PV + SV + PGx, the total score ranged from -1 to 36; mean score 12.2 (SD = 8.0). Where global item ratings indicated that test results prompted better care (n=35), the mean C-GUIDE score was 19.6 (SD = 7.2; range: 7 to 36). Where global item ratings indicated that test results may prompt better care (n=62), the mean C-GUIDE score was 8.5 (SD = 5.4; range: -1 to 26) and where global item ratings indicated that test results did not prompt better care (n=6), the mean C-GUIDE score was 7.2 (SD = 3.1; range: 2 to 10).

When the C-GUIDE score included only PV, on average, a one unit increase in the global item score was significantly associated with an increase of 6.4 in the C-GUIDE score (p < 0.05). Increase in age was associated with a decrease in C-GUIDE score of 0.002 per year (p<0.05). The presence of neurological phenotypes and diagnostic results was significantly associated with an increase in C-GUIDE score by 2.0 (p<0.05), compared to the presence of non-neurological and non-diagnostic results. When the C-GUIDE score included PV+SV, on average, a one unit increase in the global item score was associated with an increase of 7.1 in the C-GUIDE score (p < 0.05). When the C-GUIDE score included PV+SV+PGx, on average, a one unit increase in the global item score was significantly associated with an increase of 7.4 in the C-GUIDE score (p < 0.05). Sex, number of prior tests, and GS strategy (ie, singleton vs trio) were not independently associated with changes in C-GUIDE scores.

Conclusion: Aligned with the previous validation study for C-GUIDE, our findings provide further evidence that C-GUIDE measures the construct of clinical utility from the perspective of clinicians, in a rare disease population receiving GS. Specifically, the significant positive association between C-GUIDE and global item scores provides evidence of construct validity. We also provide evidence of C-GUIDE’s construct validity in the context of secondary and/or pharmacogenomic variants. Our findings suggest that C-GUIDE achieves acceptable levels of construct validity and can be integrated into studies that aim to capture the clinical utility of pediatric diagnostic genetic testing, including GS. Quantifying the clinical utility of genetic testing in standardized ways will inform efforts to optimize the use of genetic and genomic technologies in patient care.

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Beyond newborn screening: family planning implications and considerations for parents of a child with severe combined immunodeficiency

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Introduction: Severe Combined Immune Deficiency (SCID) is a rare, genetic disorder that affects 1 in 58,000 babies born each year. With all 50 states in the U.S. screening for SCID, it’s important that we support families through this life-long journey, recognizing that a family’s educational needs and support around SCID do not end with treatment, but extend across a person’s lifespan, including their family planning considerations and decisions.

With no current literature around family planning considerations, needs, and experiences for those who have a child with SCID, Expecting Health at Genetic Alliance with support from SCID Compass, a Human Resources and Services Administration (HRSA) funded program, sought to better understand the family planning needs and concerns of parents who have a child with SCID and are planning to or have grown their family.

Methods: In April 2021, we conducted 9 in-depth interviews with parents who have a child with SCID and have subsequent children or are in the process of growing their family. An interview guide was iteratively developed and utilized during all interviews. The confidential interviews lasted approximately 60 minutes and were recorded and transcribed. After all interviews were complete, a qualitative codebook was developed deductively. All transcripts were then coded and subsequently analyzed.

Results: It became apparent no two families interviewed had the same experience with SCID or family planning afterwards. Across the interviews, parents shared a range of SCID and family planning experiences from pursuing in-vitro fertilization to natural conception. Despite the variety of experiences, significant themes emerged in families’ experiences in managing a SCID diagnosis, influences on decision making and planning for additional children, and the lack of education and support from healthcare providers.

Interviewees described their different experiences of their child receiving a SCID diagnosis either through newborn screening or not. They detailed follow-up testing procedures, treatment, and long-term care. Many of these experiences were described as “scary” and “worrisome”, but interviewees also shared numerous positive experiences they had throughout the process.

Throughout the interviews, interviewees revealed many factors in the decision to have additional children after having a child with SCID. Their SCID child’s health and wellbeing, the financial cost of having another child (with or without SCID), mental health considerations, desire to have another child, and social support were all factors detailed. One interviewee highlighted the intersection of many of these issues by saying, “I was really hesitant to go through IVF because I also didn’t want my daughter to think that there was something so wrong with her that we would spend $30,000 to avoid having another child like her.”

When asked about what family planning resources were made available to them, many interviewees highlighted a lack of education and resources about having additional children after having a child with SCID. Desired resources included a social network of other families going through the same thing to share information, ideas, and experiences with as well as a personalized family planning resource for parents of a child with SCID. One interviewee described this as, “like a personalized website or brochure that talks about SCID and family planning, and whether or not you’d have one another one naturally whether or not to have another one. And then all the IVF information pertaining to testing the embryo for SCID, whether or not you want an HLA match, that would have been very helpful, because then that would all just be like, you know, together.”

Throughout the presentation, we will break down these key themes of parents’ experiences with family planning after having a child with SCID.

Conclusion: While newborn screening provides the opportunity to identify and treat babies early with a rare, genetic disorder, it is critical to support families beyond this initial screen and throughout the rest of their family planning journey. Our interviews with parents who have children with SCID highlight the unmet educational needs of parents who have a child with a rare, genetic disorder. In this presentation, we will share recommendations to support family planning considerations and decisions for families and individuals with a rare genetic disorder.

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