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(Un)standardized testing: the diagnostic odyssey of children with rare genetic disorders in Alberta, Canada

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Purpose: We provide a description of the diagnostic odyssey for a cohort of children seeking diagnosis of a rare genetic disorder in terms of the time from initial consultation to most recent visit or receipt of diagnosis, the number of tests per patient, and the types of tests received.

Methods: Retrospective chart review of 299 children seen at the Alberta Children's Hospital (ACH) Genetics Clinic (GC) for whom the result of at least one single-gene test, gene panel, or chromosome microarray analysis (CMA) was recorded.

Results: Of 299 patients, 90 (30%) received a diagnosis in the period of the review. Patients had an average of 5.4 tests each; 236 (79%) patients received CMA; 172 (58%) patients received single-gene tests and 34 (11%) received gene panels; 167 (56%) underwent imaging/electrical activity studies. The mean observation period was 898 days (95% confidence interval [CI] 791, 1004). Among patients with visits recorded prior to visiting ACH GC, 43% of the total observation time occurred prior to the GC.

Conclusion: As genomic technologies expand, the nature of the diagnostic odyssey will change. This study has outlined the current standard of care in the ACH GC, providing a baseline against which future changes can be assessed.

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INTRODUCTION

Rare genetic disorders affect a small number of people worldwide, but collectively they contribute substantially to the burden of childhood disease. Of the more than 6000 identified rare disorders, nearly 70% are exclusively childhood onset, and a further 18% have onset spanning both childhood and adulthood, meaning that 88% of all rare genetic disorders could present in childhood.[1] Children with rare genetic disorders often have decreased life expectancy, functional impairment or disability, and reduced reproductive capability.[2]

Currently, children with rare genetic disorders may be subjected to a variety of individual gene or gene panel tests, biopsies, and surgical procedures in pursuit of a diagnosis. And yet, despite extensive testing, a substantial proportion of patients may not receive a diagnosis.[3,4] This testing process is often referred to as a "diagnostic odyssey", reflecting the length of time and significant uncertainty that may be experienced by children with a suspected genetic disorder and their families. Testing patterns may be reflexive, whereby the result of each test is used to guide further inquiry, or patients may have a set of tests ordered simultaneously.[5] In Canada, the availability of specialized genetic testing may be limited and require additional funding approvals.

As diagnostic technologies evolve, the costs of genome wide sequencing (GWS), including exome sequencing (ES) and genome sequencing (GS) decrease, and more genetic disorders are identified, the potential for diagnosis may expand for some patients. Currently, the availability of GWS in Canada has been largely limited to research settings. However, some jurisdictions are moving toward offering ES in clinical settings.[6] As the availability of ES expands and moves into routine clinical practice, there is a need to better define who ES is best suited for and under what conditions.

Guidelines endorsed by the Canadian College of Medical Geneticists (CCMG) in 2015[7] to facilitate the adoption of ES into clinical practice in Canada recommend ES be considered as a second or third line testing strategy for genetic diagnosis of monogenic disorders for patients with (1) a phenotype suggestive of a monogenic disorder associated with a high degree of genetic heterogeneity, (2) for patients with a nonspecific phenotype, or (3) for patients with a specific phenotype that is not genetically heterogeneous, but for whom targeted gene testing has not yielded a diagnosis.[7]

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A critical piece in understanding the impact of this testing approach is having a clear picture of the number of types of investigations that patients currently undergo and where in the health system these tests occur, so that it will be possible to clearly identify the elements of testing that may be avoided by a change in policy or practice guidelines and where in the health system those changes are likely to occur.

Evidence relating to the length of diagnostic odyssey is limited in part by the length of study follow up; currently available literature reports average observation times ranging from one year up to eight years.[8–13] Within this body of literature, the average time to diagnosis is difficult to ascertain due to differences in study reporting. Further, the generalizability of the current findings is limited by variations in target population and inclusion criteria. Available research has largely been focused on phenotypic presentation[6,9,12–16] or utilized study inclusion criteria, such as test naivety[10,11] or enrollment in complex care programming[17] that would not be relevant when considering implementation at the clinic and health systems level.

The present study describes the diagnostic odyssey of a cohort of pediatric patients seen at the Alberta Children's Hospital Genetics Clinic. The aim of the study was to look at a broad range of patients who may be eligible for ES based on CCMG guidelines and describe their diagnostic journey in terms of the length of time elapsed and the amount of time accruing in different diagnostic intervals, as well as the number and types of diagnostic testing and consultations per patient, and the relative proportions of observation time occurring before and after the first visit to the Genetics Clinic. This information provides data that are essential for understanding the diagnostic odyssey of patients who may be eligible for ES as it becomes more widely available in Canada through the expansion of domestic laboratory capacity.

MATERIALS AND METHODS

Ethics statement

The study was approved by the University of Calgary Research Ethics Board (REB16–0871). A waiver of individual consent was granted by the board due to the minimal risk to patients associated with inclusion in the review and it was deemed not practical, reasonable, or feasible to obtain individual consent. Individual patient data were de-identified.

The study sample was drawn from a full list of patients attending the Alberta Children's Hospital (ACH) Genetics Clinic (GC) between 1 January 2010 and 1 January 2016. ACH is a pediatric tertiary care hospital serving southern Alberta, southwestern Saskatchewan, and southeastern British Columbia, an area with approximately 2.5 million residents; approximately 97,000 patients visit ACH per year.[18] All GC patients were referred from other primary, secondary, or tertiary health-care providers. During the time period covered by the chart review, publicly funded ES was not available to patients at ACH.

Paper records maintained by the GC were accessed and manually searched for evidence relating to the number of visits, consultations, investigations, test results, and referrals. Information contained in the charts was not standardized in terms of presentation; however, because charts were compiled by the GC and were not general medical records, all content included was assumed to be relevant to the diagnostic odyssey and was recorded.

Within the genetics clinic, individual identification numbers are assigned to each patient. The structure of the numbering system allowed researchers to develop a sampling frame of patients with clinic identifiers generated in the each of the years covered by the study period. Charts were randomly selected from the full sampling frame using a random number generator; screening and selection continued until a target sample size of 300 was achieved. A total of 519 paper charts were screened and data were recorded for 300 charts; data entry for one chart was incomplete and this record was subsequently excluded, leaving a final sample size of 299. Data entry was performed by two research assistants (F.O., B.S.). Double data entry was completed for 10% ($n = 52$) of all charts retrieved and additional quality assurance performed by two independent reviewers (C.M-I., K.V.M.) for 5% ($n = 12$) of single entered included charts. Of included charts that were double entered, interrater agreement on patient age, sex, and diagnosis status was ≥96%. Agreement on number of visits was 62%; however, the majority of discrepancies were a difference of one visit. Disagreements in the total number of visits with a difference greater than one visit were recorded in 15% of cases; no differences larger than three were recorded. The frequency and magnitude of differences in the number of visits recorded reduced as double data entry progressed; in the second half of the double entered sample no differences in the total number of visits greater than one were noted and overall percent agreement rose to 71%. This reflects both the change in study protocol as well as learning through discussion and consultation that occurred over the course of the data entry period. Differences identified in double data entry were resolved through discussion and additional review of the chart.

Reasons for exclusion were the first recorded visit occurred prior to 1 January 2010 or after 1 January 2016 ($n = 15$); the results of at least one single-gene test, gene panel, or chromosome microarray analysis were not recorded in the chart ($n = 203$); or the named patient selected for inclusion was not found in the corresponding chart number retrieved ($n = 2$). Exclusion criteria were applied sequentially. The first criterion met is the only one counted as reason for exclusion; some patients may have met more than one criterion.

Standardized data entry was performed in REDCap, an electronic data entry platform. Details entered included eligibility screening questions, patient background information (i.e., sex, birth year), visit locations and dates, test types and dates related to the test order, sample collection, return of results to the clinic and/or patient, diagnostic status, diagnosis

Table 1 Age at first recorded diagnosis-related visit to any primary, secondary, or tertiary health-care provider and first visit to ACH GC.

Age	First recorded visit to any health-care provider, female, *n* (%)	First visit to ACH GC, female, *n* (%)	First recorded visit to any health-care provider, male, *n* (%)	First visit to ACH GC, male, *n* (%)
0 to 1 years	67 (51)	56 (43)	71 (42)	61 (36)
>1 and ≤5 years	34 (26)	39 (30)	59 (35)	44 (26)
>5 and ≤10 years	18 (14)	19 (15)	29 (17)	40 (24)
>10 years and up	12 (9)	17 (13)	9 (5)	23 (14)
Total	131	131	168	168

ACH GC Alberta Children's Hospital Genetics Clinic.

type, and summarized clinical notes. Data were analyzed using STATA.[19] To permit statistical analysis, data were entered as quantitative variables where possible. Analysis consisted of descriptive statistics, *t*-tests, $\chi 2$ analyses, Fisher's exact test, and Kruskal–Wallis H test.

RESULTS

Demographics and diagnoses

The final sample consisted of 168 (56%) males and 131 (44%) females. The age of first recorded visit to any primary, secondary, or tertiary health-care providers for an issue related to their pursuit of a diagnosis, and age at first visit to ACH GC is presented by sex in Table 1. Differences in age at first visit to any health-care provider ($p = 0.148$) and at first visit to ACH GC ($p = 0.223$) were not statistically significant. Overall, the age at first visit to any provider was ≤5 years for over 75% of patients in the sample. At the first visit to ACH GC, approximately 67% of patients were ≤5 years of age.

Of 299 included patients, 200 (67%) had diagnosis-related visits to primary, secondary, or tertiary health-care providers prior to their first visit to ACH GC recorded in their chart. In the time period covered by the chart review, 181 (61%) did not receive a diagnosis of a rare genetic disorder, 90 (30%) patients received a diagnosis, and 28 (9%) patients received results of uncertain clinical significance or findings not likely to contribute to the current phenotype. No statistically significant differences in diagnosis status were observed according to gender (Fisher's exact test = 0.138), age at first visit to any health-care provider (Fisher's exact test = 0.186), age at first visit to ACH GC (Fisher's exact test = 0.103), or whether visits prior to the first ACH GC were recorded in the chart (Fisher's exact test = 0.610).

Number of diagnosis-related tests or health-care visits per patient

The total number of tests or visits per patients is summarized according to diagnosis status in Fig. 1. For the 299 patients included in the sample, 1622 diagnosis-related tests or visits were recorded, translating to an average of 5.4 visits per patient overall. On average, patients who did not receive a diagnosis had 4.4 tests or visits (median = 3), patients who received a diagnosis had 6.7 (median = 6), and those with an uncertain diagnosis had 7.5 (median = 6) (Kruskal–Wallis H test: $p < 0.001$) (Supplementary Table S1).

Number and type of tests and investigations

The most commonly used test among the reviewed sample was chromosome microarray analysis (CMA), with 236 (79%) of all patients receiving at least one CMA. Details of all test and investigation types recorded are provided in Supplementary Table S2. The next most common test type was single-gene tests, which were provided to 172 (58%) patients, and imaging or electrical activity studies (i.e., magnetic resonance image [MRI], ultrasound, radiograph, electroencephalogram [EEG], electrocardiogram [ECG]), undergone by 167 (56%) patients. On average, patients who had biochemical tests had five each, those who underwent imaging or electrical activity studies had two each, and those who had single-gene tests had approximately two each. For cytogenetic testing, chromosome breakage analysis, and biopsy/surgical procedures, the average number of tests per patient is approximately one.

Of the 254 single-gene tests ordered, 71 different types were identified. The five most common single-gene tests observed were related to testing for fragile X (FRAXA polymerase chain reaction [PCR]) (82), Prader–Willi/Angelman syndrome (PWS/AS methylation-specific multiplex ligation-dependent probe amplification [MS-MLPA]) (30), Rett syndrome (*MECP2* sequencing) (17), and myotonic dystrophy (DM1 screen) (13). A total of 488 biochemical tests were recorded, of these 55 unique test types were identified, with the most commonly observed tests being urine organic acid analysis (102), plasma amino acid analysis (80), and urine metabolic screen (59). Of 40 gene panels conducted, 31 different types of panels were identified. In 15 charts, it was noted that ES had been recommended for the patient; of these, 11 had enrolled in a research study offering ES and 2 sought ES from private laboratories.

Observation time and time to diagnosis

The mean time from first visit to any provider to final observation was 898 days (95% confidence interval [CI] 791, 1004) (2.25 years) for all patients (Table 2). For patients with a diagnosis, the period from first recorded visit to any

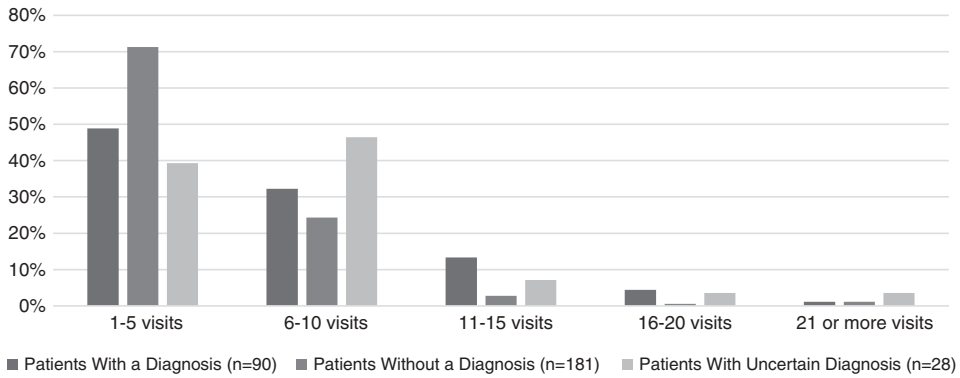

Fig. 1 Total number of tests or visits per patient by diagnosis status, proportion of patients ($n = 299$).

Table 2 Time in days from first visit to diagnosis or final observation according to diagnosis status.

Days elapsed[a]	Mean (SE)	Median	95% CI	
All individuals ($n = 299$)				
First visit to any health-care provider to final observation	898 (54)	595	791	1004
Patients with a diagnosis ($n = 90$)	938 (92)	719	754	1121
Patients with no diagnosis ($n = 181$)	806 (69)	497	670	942
Patients with uncertain diagnosis ($n = 28$)	1360 (199)	1199	951	1769
First visit to ACH GC to diagnosis or final observation	483 (32)	285	421	546
Patients with a diagnosis ($n = 90$)	586 (57)	452	472	700
Patients without a diagnosis ($n = 181$)	388 (39)	176	310	465
Patients with uncertain diagnosis ($n = 28$)	769 (104)	563	555	983
Individuals with visits prior to ACH GC recorded ($n = 200$)				
First visit to any health-care provider to first visit to ACH GC	619 (64)	293	492	745
Patients with a diagnosis ($n = 61$)	519 (109)	154	300	738
Patients without a diagnosis ($n = 118$)	640 (85)	315	472	809
Patients with uncertain diagnosis ($n = 21$)	788 (208)	546	354	1222
First visit to ACH GC to diagnosis or final observation	486 (40)	296	408	563
Patients with a diagnosis ($n = 61$)	619 (71)	562	478	761
Patients without a diagnosis ($n = 118$)	383 (51)	157	283	483
Patients with uncertain diagnosis ($n = 21$)	672 (115)	504	432	912

ACH GC Alberta Children's Hospital Genetics Clinic, *CI* confidence interval.
[a]Rounded to nearest whole day.

provider to receipt of a diagnosis was 938 days (95% CI 754, 1121), compared with an observation period of 806 days (95% CI 670, 942) for patients who did not receive a diagnosis and 1360 days (95% CI 951, 1769) for patients with uncertain diagnoses. For patients in our sample, this translates to an observation period that is 131 days longer for those with a diagnosis compared with those without a diagnosis.

To identify where in the health system this time accrued, we also calculated how much of the total time accrued from first visit to diagnosis or final observation was comprised of visits and investigations carried out prior to attending ACH GC and how much of the total time accrued after the patient first attended ACH GC (Table 2). Among only those patients with visits recorded prior the first visit to ACH GC, the mean number of days elapsed from the first visit recorded with any provider to the time that the patient was seen at ACH GC for the first time was 619 days (95% CI 492, 745). Among individuals who went on to receive a diagnosis, this time period is shorter compared with those who did not receive a diagnosis, with observation times of 519 days (95% CI 300, 738) and 640 (95% CI 472, 809), respectively.

Among this same subset of patients with visits recorded before the first visit to ACH GC, the average total time from first visit to ACH GC to diagnosis or final observation was 486 days (95% CI 408, 563). For patients who did not receive a diagnosis, this time was shortest, at 383 days (95% CI 283, 483). For patients who went on to receive a diagnosis, mean observation time was days (95% CI 478, 761) and for those that received an uncertain diagnosis, mean observation time was 672 days (Table 2). These results are comparable with those of the full sample (Table 2). The time from first visit to ACH GC to diagnosis or final observation for patients with no

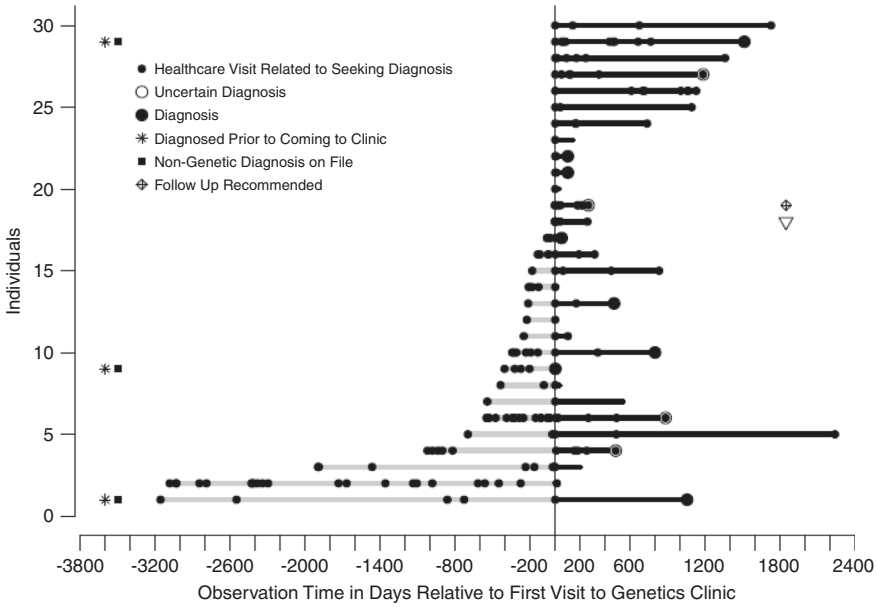

Fig. 2 Number of visits per patient, observation time in days before and after first visit to Alberta Children's Hospital Genetics Clinic (ACH GC) and patient diagnosis status for a sample of 30 patients.

visits prior to ACH GC follow a similar pattern, but are not presented separately due to the small sample sizes as across different categories of diagnoses.

Figure 2 provides a visual illustration of the timeline for a random sample of 30 patients in terms of the number of visits occurring before and after the first visit to ACH GC and individual diagnosis status. When considering only those patients for whom visits were recorded both before and after the first visit to ACH GC, approximately 43% of the observation window occurred prior to the first visit to ACH GC, and 57% occurred after the first visit to ACH GC (Supplementary Table S3). For patients who received a diagnosis, 64% of their observation period occurred after their first visit to ACH GC. Among patients who did not receive a diagnosis and those with uncertain diagnoses, this proportion was 52% and 56% respectively.

Of 90 diagnoses, 75 different types were identified. Of the 12 diagnoses that were common to more than one individual, 10 were shared by only two individuals, one diagnosis was common to three individuals, and one was common to four individuals. Forty-nine (54%) diagnoses were related to single-gene disorders and 35 (38%) were chromosomal abnormalities (Table 3). The remaining seven (8%) "other" diagnoses are made up of epigenetic/teratogenic disorders and miscellaneous diagnoses. The mean total time to diagnosis for single-gene disorders and chromosomal abnormalities was 850 days (2.3 years) and 1003 days (2.7 years) respectively. This time period was longer for patients with "other" diagnoses, at a mean of 1232 days (3.4 years). A similar trend is observed for the time elapsed between the first recorded visit to any provider and the first visit to ACH GC, with a longer time frame for patients diagnosed with a chromosomal abnormality compared with a single-gene disorder and for "other diagnoses". In contrast, following the first visit at ACH GC, patients with "other" diagnoses, received a diagnosis in 148 days on average (approximately 5 months), compared with a year for patients with other diagnosis types (Table 3). The differences in mean total observation time and the time from first visit to any health-care provider to first ACH GC visit were not statistically significant across the diagnosis types. However, differences across diagnosis groups in terms of the observation time from the first visit to ACH GC to receipt of diagnosis are statistically significant ($p < 0.5$); this is likely due to the shorter observation time for individuals with diagnoses in the "other" category.

DISCUSSION

The availability of GWS in routine clinical practice has the potential to radically alter the standard of care for patients pursuing a diagnosis of a rare genetic disorder. Currently, GWS technologies like ES have been used as a last resort, following an often extensive diagnostic odyssey. As ES becomes more accessible in Canada, it is increasingly important to ensure that the application of this technology is optimized. A first step in understanding the optimal position of ES in the diagnostic trajectory is to understand the patterns of serial or reflexive testing that patients have typically undergone as the standard of care. This can lead to a more informed discussion around which elements of the odyssey ES may feasibly replace, and which patients are most likely to benefit.

Our study confirmed and quantified the long duration of the diagnostic odyssey for children with suspected rare genetic disorders in a Canadian setting. On average, the odyssey spanned 2.5 years and involved 5.4 visits or tests per

Table 3 Total number of diagnoses and observation times according to diagnosis type and recorded visits prior to ACH GC.

		All patients ($n = 90$)				Patients with visits prior to ACH GC recorded ($n = 61$)			
		Total observation time in days, all patients		Time elapsed between first visit ACH GC to final observation in days		Time elapsed between first visit to any provider to ACH GC in days		Time elapsed between first visit ACH GC to final observation in days	
Diagnosis type	**Diagnoses, *n* (%)**	**Mean (SE)**	**Median (min–max)**	**Mean (SE)**	**Median (min–max)**	**Mean (SE)**	**Median (min–max)**	**Mean (SE)**	**Median (min–max)**
Single gene	49 (54)	850 (115)	728 (1–4213)	607 (74)	562 (1–2462)	384 (120)	154 (2–3158)	747 (99)	665 (1–2462)
Chromosomal	34 (38)	1003 (151	733 (4–3247)	647 (102)	453 (1–1965)	527 (176)	129 (1–3247)	591 (117)	434 (1–1965)
Other	7 (8)	1232 (499)	514 (331–3679)	148 (66)	57 (1–430)	1084 (533)	405 (71–3622)	148 (66)	57 (1–430)
Total	90	938 (92)	719 (1–4213)	586 (57)	452 (1–2462)	519 (109)	150 (1–3622)	619 (71)	532 (1–2462)

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patient. However, this varied across diagnostic status and diagnosis type.

Overall, 30% of the patients included in our sample received a diagnosis through serial or reflexive testing, the current standard of care.

Our results are broadly comparable with other studies in terms of the length of the diagnostic odyssey, which ranges from one to eight years in the literature.[9–13,20] Variation in the ways that elements of the odyssey are recorded make it difficult to draw direct comparisons; however, our estimates of the number of tests and visits per patient are within the ranges reported in the literature. For example, a Canadian cohort of 100 children that met clinical criteria for CMA, and were selected to receive GS, had an average of three genetic tests prior to study enrollment, with a range of 1 to 13 tests.[21] The later study did not report on inpatient, clinic visits or imaging studies. In contrast, van Nimwegen et al. found that over the course of three years, among their sample of 50 complex pediatric neurology patients, the mean number of physician visits was 16, the mean number of phone/email consultations was 14, and the mean number of diagnostic tests was 16.[12] In Australia, Thevenon et al. conducted a retrospective review of 43 patients with severe neurodevelopmental delays, and found that the number of genetic diagnostic tests per patient range from 0 to 9, and metabolic tests range from 0 to 20, although no associated time period was reported.[14] Also in Australia, Tan et al. report on the diagnostic odyssey of 44 children aged 2–18 years with presentation suggestive of monogenic disorders, who had at least one assessment by a clinical geneticist but had not had a single-gene test or gene panel. In this study, the mean number of tests per patient was 19. Each child also had a mean of four clinical genetics visits and four consultations with nongenetics specialists.[11] In this case, the mean time from tertiary presentation to genetics assessment was 13 months and the mean time from genetics assessment to ES report was 6 months.[11]

In the United States, in a retrospective analysis of 500 consecutive charts with a predominantly pediatric sample (>90% pediatric patients), Shashi et al. recorded 1–8 visits per patient and up to 33 diagnostic tests. In this study, 72% of patients were diagnosed on first visit.[5] However, in this study some diagnoses were based on clinical assessment only,[11] and the inclusion criteria were designed to reflect the clinic population as a whole rather than according to phenotypic category, clinical presentation or testing history.

We note conflicting results in the literature with respect to the nature of the diagnostic odyssey for patients who receive a diagnosis. Oei et al. found that patients with no diagnosis underwent significantly more testing in the time period covered by their review compared with those who received a diagnosis.[17] In contrast, Shashi et al. found that patients with a diagnosis had fewer tests compared with those without a diagnosis.[5] Our findings are consistent with the latter results, which indicate that patients with no diagnosis had fewer tests or visits on average, despite having a longer diagnostic

odyssey overall. One explanation for this apparent contrast may be due to differences in the way that visits and tests were counted in each of the studies. All three studies employed a retrospective chart review methodology and data are likely to have been recorded in the charts differently in different settings, and data extraction procedures may have introduced other biases.

A key finding in our study relates to the amount of time accrued in the diagnostic odyssey before patients arrive in the genetics clinic. In particular, patients with no diagnosis spent a greater proportion of their diagnostic odyssey in settings outside the ACH GC, compared with those who received a diagnosis. This suggests that decreasing referral time to the genetics clinic could have more on an impact on reducing the overall length of the odyssey for this group of patients. The proportion of the diagnostic odyssey spent within the ACH GC, or after the first visit to the ACH GC, was 60% for patients who went on to receive a diagnosis. For these patients, a reduction in the overall diagnostic odyssey may be realized through more timely access. The proportion of the odyssey accruing prior to the first visit to the ACH GC reflects the complex nature and structure of the referral pathway, which has not been well documented in the literature. Adopting new clinical guidance around eligibility and implementation of GWS in routine clinical practice will require an understanding of the referral pathway to ensure that assumptions around the extent to which serial testing occuring outside of specialist genetics clinics can be averted or replaced with earlier adoption of GWS are consistent with current clinical pathways and standards of care.

Our study inclusion criteria of having the result of a single-gene test, gene panel, or chromosome microarray analysis recorded in the chart means that if the CCMG guidelines were adopted, the remaining 209 children who did not obtain a diagnosis could be candidates for ES.

Despite providing some new insights, our study has some limitations. Our paper-based chart review relied on provider reporting and recording. Case files and notes were more extensive for some patients than others and connecting visits to tests and dates was a particular challenge. It is for this reason that we have reported tests and visits together rather than separating out visits that were consultations only. We also encountered undated information in charts and made inferences about the timing and ordering of tests and return of results by triangulating with pieces of information within each chart. The amount of information about tests and visits with health-care providers prior to the first visit at ACH GC was also limited and may be incomplete. The retrospective nature of the review and the inclusion criteria applied means that some patients included in this study and recorded as having no diagnosis may have gone on to receive a diagnosis.

This study adds to a limited body of literature describing the diagnostic odyssey of children with suspected rare genetic disorders. Strengths of our approach are that the inclusion criteria align with CCMG recommendations for the clinical application of ES. Basing the inclusion criteria on testing history rather than phenotypic presentation means that the results may be more broadly generalizable to the population of patients seen at other genetics clinics. This study is the first to consider the proportion of the diagnostic odyssey that is accrued in different areas of the health system. Further research is required to assess the relative costs and potential cost savings that may be realized as a result of changes to eligibility criteria for ES and implementation in routine clinical practice and to describe the referral pathway in more detail. Understanding barriers and facilitators to accessing services in specialty clinics may help decision makers identify strategies to reduce the portion of the diagnostic odyssey that occurs prior to patients arriving in the genetics clinic.

Conclusion

As GWS technologies advance, adoption into routine clinical practice is becoming a reality in many jurisdictions. Though costs associated with ES have been decreasing, they remain high. In the context of limited health-care resources, it is important to understand how to optimize its use. This study has outlined the current standard of care in the ACH GC, providing a baseline against which future changes can be assessed.

SUPPLEMENTARY INFORMATION

The online version of this article (https://doi.org/10.1038/s41436-020-00975-0) contains supplementary material, which is available to authorized users.

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DISCLOSURE

The authors declare no conflicts of interest.

REFERENCES

1. Wakap SN. et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28:165–173.
2. Ferreira CR. The burden of rare diseases. Am J Med Genet A. 2019;179: 885–892.
3. Chae JH, et al. Utility of next generation sequencing in genetic diagnosis of early onset neuromuscular disorders. J Med Genet. 2015; 52:208–216.
4. Kingsmore SF, et al. Adopting orphans: comprehensive genetic testing of Mendelian diseases of childhood by next-generation sequencing. Expert Rev Mol Diagn. 2011;11:855–868.

5. Shashi V, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2013;16:176–182.
6. Tsiplova K, et al. A microcosting and cost–consequence analysis of clinical genomic testing strategies in autism spectrum disorder. Genet Med. 2017;19:1268.
7. Boycott K, et al. The clinical application of genome-wide sequencing for monogenic diseases in Canada: position statement of the Canadian College of Medical Geneticists. J Med Genet. 2015;52:431–437.
8. Dragojlovic N, et al. The cost trajectory of the diagnostic care pathway for children with suspected genetic disorders. Genet Med. 2020;22: 292–200.
9. Soden SE, et al. Effectiveness of exome and genome sequencing guided by acuity of illness for diagnosis of neurodevelopmental disorders. Sci Transl Med. 2014;6:265ra168.
10. Stark Z, et al. Prospective comparison of the cost-effectiveness of clinical whole-exome sequencing with that of usual care overwhelmingly supports early use and reimbursement. Genet Med. 2017;19:867.
11. Tan TY, et al. Diagnostic impact and cost-effectiveness of whole-exome sequencing for ambulant children with suspected monogenic conditions. JAMA Pediatr. 2017;171:855–862.
12. van Nimwegen KJM, et al. The diagnostic pathway in complex paediatric neurology: a cost analysis. Eur J Paediatr Neurol. 2015;19:233–239.
13. Monroe GR, et al. Effectiveness of whole-exome sequencing and costs of the traditional diagnostic trajectory in children with intellectual disability. Genet Med. 2016;18:949–956.
14. Thevenon J, et al. Diagnostic odyssey in severe neurodevelopmental disorders: toward clinical whole-exome sequencing as a first-line diagnostic test. Clin Genet. 2016;89:700–707.
15. Palmer EE, et al. Integrating exome sequencing into a diagnostic pathway for epileptic encephalopathy: evidence of clinical utility and cost effectiveness. Mol Genet Genom Med. 2018;6:186–199.
16. Schofield D, et al. Cost-effectiveness of massively parallel sequencing for diagnosis of paediatric muscle diseases. NPJ Genom Med. 2017;2:1–7.
17. Oei K, et al. Genetic testing among children in a complex care program. Children. 2017;4:42.
18. Alberta Children's Hospital Foundation. Alberta Children's Hospital Foundation: our hospital. 2020. http://www.childrenshospital.ab.ca/site/PageNavigator/hospital/our_hospital.
19. StataCorp. Stata statistical software: release 12. 2011, StataCorp LP: College Station, TX.
20. Dragojlovic N, et al. The cost and diagnostic yield of exome sequencing for children with suspected genetic disorders: a benchmarking study. Genet Med. 2018;20:1013.
21. Stavropoulos DJ, et al. Whole-genome sequencing expands diagnostic utility and improves clinical management in paediatric medicine. NPJ Genom Med. 2016;1:15012.