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Genetic care in geographically isolated small island communities: 8 years of experience in the Dutch Caribbean

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Abstract

Worldwide, there are large inequalities in genetic service delivery. In 2011, we established a bi-annual joint pediatric-genetics clinic with a visiting clinical geneticist in the Dutch Caribbean. This retrospective study evaluates the yield of diagnostic testing and the clinical utility of a diagnosis for patients with rare diseases on these relatively isolated, resource-limited islands. A total of 331 patients that were referred to the clinical geneticist between November 2011 and November 2019 and had genetic testing were included in this study. A total of 508 genetic tests were performed on these patients. Microarray, next-generation sequencing gene panels, and single-gene analyses were the most frequently performed genetic tests. A molecularly confirmed diagnosis was established in 33% of patients ($n = 108$). Most diagnosed patients had single nucleotide variants or small insertions and/or deletions (48%) or copy number variants (34%). Molecular diagnostic

yield was highest in patients referred for seizures and developmental delay/intellectual disability. The genetic diagnosis had an impact on clinical management in 52% of patients. Referrals to other health professionals and changes in therapy were the most frequently reported clinical consequences. In conclusion, despite limited financial resources, our genetics service resulted in a reasonably high molecular diagnostic yield. Even in this resource-limited setting, a genetic diagnosis had an impact on clinical management for the majority of patients. Our approach with a visiting clinical geneticist may be an example for others who are developing genetic services in similar settings.

KEYWORDS
caribbean, clinical genetics, clinical utility, diagnostic yield, rare diseases

1 | INTRODUCTION

Rare diseases are estimated to affect at least 3.5%–5.9% of the global population (Nguengang Wakap et al., 2020). Most rare diseases have a genetic basis (71.9%) and have an exclusively pediatric-onset (69.9%) (Nguengang Wakap et al., 2020). Recent genetic technological advances including exome and genome sequencing result in an increased diagnostic yield for patients with suspected genetic disorders (Gilissen et al., 2014; Lionel et al., 2018; Stark et al., 2016; Stavropoulos et al., 2016; Yang et al., 2014) and improve clinical management and reproductive decision making (Malinowski et al., 2020). However, due to global inequalities in genetic service delivery, patients with rare diseases in lower-resource countries have limited access to genetic testing and counseling and thus remain undiagnosed. Barriers to delivering genetic services in resource-limited areas include a lack of adequately equipped diagnostic laboratories, a shortage of clinical geneticists and genetic counselors, logistic and financial barriers for patients, and a lack of knowledge about genetic disorders among healthcare providers (Angural et al., 2020; Tekola-Ayele & Rotimi, 2015; Yip et al., 2019; Zhong et al., 2018).

For small islands like those of the Dutch Caribbean, the delivery of genetic services is further complicated by their remote geography and small population sizes. The Dutch Caribbean consists of six islands located in the Caribbean sea: Aruba, Curacao, and St. Maarten (constituent countries within the Kingdom of the Netherlands) and Bonaire, St. Eustatius, and Saba (special municipalities of the Netherlands). Although these islands are high-income economies, they face several unique challenges due to their small size and relative remoteness, including healthcare, infrastructure, and environmental challenges (Maria et al., 2020). The largest island, Curaçao, has a population of only 156,223 (Central Bureau of Statistics Curaçao, 2020). Providing highly specialized medical care for a small population means low demand and therefore disproportionally high costs (Maria et al., 2020). In addition, with low patient volumes, medical specialists may not be able to maintain and improve the knowledge and skills needed for a high degree of specialization (Croes, 2015).

Although available resources differ per island until recently there was no local clinical genetics service on any of the six Dutch Caribbean islands. Local pediatricians occasionally sent blood samples to diagnostic laboratories abroad, for example, to confirm a clinical diagnosis of Down syndrome (usually by karyotyping). Alternatively, patients were sent abroad to a tertiary hospital (in the Netherlands or Colombia) for diagnostic evaluation, including genetic testing. This was, however, only possible on the strict indication because of the high associated costs (including transportation, hospital admission, and accommodation for the accompanying family members). To increase access to genetic testing and counseling for the pediatric population of the Dutch Caribbean, a bi-annual joint pediatric-genetics clinic with a visiting clinical geneticist was established in 2011. Here, we report the outcomes of this clinical genetics service, including the diagnostic yield as well as the impact of a genetic diagnosis on clinical management in this resource-limited setting.

2 | METHODS

2.1 | Setting

In 2011, a bi-annual joint pediatric-genetics clinic with a visiting Dutch clinical geneticist (MvH) was established in the Dutch Caribbean. Patients were referred by the local pediatrician for a clinical genetic evaluation at the outpatient pediatric clinics of the Curacao Medical Center (previously Sint-Elisabeth Hospital), Dr. Horacio E. Oduber Hospital in Aruba, Fundashon Mariadal in Bonaire, and St. Maarten Medical Center. Patients from the two smallest islands (Saba and St. Eustatius) were referred to the pediatric-genetics clinics at St. Maarten Medical Center. During the genetic consultations, medical and family histories were obtained, followed by a detailed (dysmorphologic) physical examination. If genetic testing was indicated, biological samples were shipped to one of the accredited university laboratories in the Netherlands where DNA was extracted from peripheral blood or buccal cells for genetic testing. Occasionally, genetic testing (mainly microarray analysis) was

requested by the local pediatrician prior to the visit of the clinical geneticist to speed up the diagnostic process. In addition, genetic testing could be requested prior to the visit of the clinical geneticist after consultation between the pediatrician and the clinical geneticist by telephone or email, for example, when a neonate or child was critically ill.

Genetic testing was performed at the departments of Genome Diagnostics of the Amsterdam University Medical Centers (Amsterdam UMC) and the Utrecht University Medical Center (UMC Utrecht). Genetic tests that were not available at these laboratories (specific genes or gene panels) were performed at one of the other five accredited university laboratories in the Netherlands. Costs of genetic testing were reimbursed by the local health insurance, although financial restrictions had to be taken into account. Trio exome sequencing (ES) was not routinely offered because of the high associated costs. To further keep costs at a minimum, all next-generation sequencing (NGS) gene panels were initially only performed in the index patient. Subsequently, segregation analysis in the parents/family of the affected individual was performed if variants of unknown significance (VUS) were identified. However, this was not always possible because of financial restrictions from local health insurance or because parental samples were not available. Abnormal genetic test results were communicated to the caregivers and/or patients by the clinical geneticist upon a follow-up visit. As the clinical geneticist visits only two times a year, the results were sometimes already communicated by the local pediatrician and discussed again during the next visit of the clinical geneticist.

2.2 | Study design and patient selection

We performed a retrospective cohort study of patients in the Dutch Caribbean referred to the visiting Dutch clinical geneticist between November 2011 and November 2019. A total of 48 clinics were held on the four different islands during this period (Table 1). All children (age < 18 years) that were referred to the genetics clinic and had genetic testing were consecutively included in this study. We also included patients that were ≥18 years if they were referred by their pediatrician. In addition, we included critically ill neonates who deceased before they could be evaluated by the clinical geneticist. In those cases, genetic testing was advised by the clinical geneticist during electronic consultation and requested by the pediatrician shortly after birth (or in one case performed in both parents). Caregivers subsequently had a consultation with the clinical geneticist to discuss the results. To avoid overestimation of the diagnostic yield, we did not include siblings with the same molecularly confirmed diagnosis as the proband. Over the years, a few adults had been referred to the clinical geneticist (mostly oncogenetic and cardiogenetic referrals). These patients were, however, excluded from the present study. Since presymptomatic genetic testing is not (yet) covered by local insurance companies, we also excluded healthy children that were referred for genetic testing because of their family history. Previously diagnosed patients who were referred for additional counseling were also excluded.

Informed consent to publish medical data was obtained from the caregivers of patients with a diagnosis. The caregivers of 12 patients did not give permission and these patients were, therefore, not included in this study. If the caregivers of a patient could not be

TABLE 1 General characteristics of the Kingdom of the Netherlands

	Constituent countries				Special municipalities of the Netherlands		
	The Netherlands	Aruba	Curaçao	St. Maarten	Bonaire	St. Eustatius	Saba
Population	17,475,415[a]	112,190[b]	153,671[c]	42,577[d]	21,745[e]	3,142[e]	1,918[e]
Area[f]	41,543 km^2	180 km^2	444 km^2	34 km^2	288 km^2	21 km^2	13 km^2
GNI per capita (US$)[g]	51,060 (2020)	27,120 (2017)	17,140 (2020)	27,680 (2018)	—	—	—
Number of clinical genetics visits (2011–2019)	—	15	16	3	14	—	—

[a]On January 1st, 2021. Statistics Netherlands, Population; key figures. https://opendata.cbs.nl/statline/#/CBS/en/dataset/37296eng/table?ts=1640263768026. Accessed 23 December 2021.
[b]On January 1st, 2020. Central Bureau of Statistics Aruba, Quarterly Demographic Bulletin 2020. https://cbs.aw/wp/index.php/2020/12/17/quarterly-demographic-bulletin-2019-2/. Accessed 23 December 2021.
[c]On January 1st, 2021. Central Bureau of Statistics Curaçao, Population Tables. https://www.cbs.cw/population-tables. Accessed 23 December 2021.
[d]On January 1st, 2021. Department of Statistics Sint Maarten, Population Estimates and Vital Statistics 2021. http://stats.sintmaartengov.org/. Accessed 23 December 2021.
[e]On January 1st, 2021. Statistics Netherlands, Caribbean Netherlands; population, sex, age and country of birth. https://opendata.cbs.nl/statline/#/CBS/en/dataset/84712ENG/table?ts=1606311418329. Accessed 23 December 2021.
[f]Government of the Netherlands, What are the different parts of the Kingdom of the Netherlands? https://www.government.nl/topics/caribbean-parts-of-the-kingdom/question-and-answer/what-are-the-different-parts-of-the-kingdom-of-the-netherlands. Accessed 23 December 2021.
[g]The World Bank, GNI per capita, Atlas method (current US$). https://data.worldbank.org/indicator/ny.gnp.pcap.cd?year_high_desc=truel. Accessed 23 December 2021.

TABLE 2 Molecular diagnoses: single nucleotide variants and small insertions and/or deletions

No.	Sex	Phenotype	Variant	Zygosity; inheritance	Transcript	CI	Associated condition, inheritance pattern [MIM number]
Diagnostic test: targeted or exome based NGS gene panels							
1	M	ID, hyperthyroidism	*THRB* c.1286G > A, p.(Arg429Gln)	het; unk	NM_001252634.1	LP	Thyroid hormone resistance, AD [188570]
50	F	ID, microcephaly, epilepsy, strabismus, facial dysmorphism	*DYRK1A* c.1399C > T, p.(Arg467*)	het; unk	NM_001396.4	P	Autosomal dominant mental retardation 7, AD [614104]
51	F	Short stature, ASD, pulmonary stenosis, webbed neck, facial dysmorphism	*SOS1* c.512 T > G, p.(Val171Gly)	het; unk	NM_005633.3	LP	Noonan syndrome 4, AD [610733]
65	M	ID, microcephaly, short stature, facial dysmorphism	*ASXL3* c.3039 + 1G > T	het; unk	NM_030632.3	P	Bainbridge-Ropers syndrome, AD [615485]
74	F	ID, DD, microcephaly, agenesis of the corpus callosum	*SOX11* c.877dup, p.(Leu293Profs*105) (novel)	het; unk	NM_003108.3	LP	Coffin-Siris syndrome 9, AD [615866]
127	F	Cleft palate, cataract	*BCOR* c.254del, p.(Pro85Argfs*25) (novel)	het; unk	NM_017745.5	P	Oculofaciocardiodental syndrome, XLD [300166]
131[a]	F	ID, DD, short stature, ataxia, nystagmus, hypodontia	*POLR3B* c.1568 T > A, p.(Val523Glu)	hmz; mat/pat	NM_018082.5	P	Hypomyelinating leukodystrophy 8, AR [614381]
133[b]	M	ID, facial dysmorphism	*USP7* c.3202 + 1G > T (novel[c])	het; dn	NM_003470.2	LP[d]	Hao-Fountain syndrome, AD [616863]
164	M	ID, facial dysmorphism, sialorrhea	*ATRX* c.7367_7371del, p.(Met2456Argfs*40) (novel)	hem; dn	NM_000489.4	LP	X-linked mental retardation-hypotonic facies syndrome, XLR [309580]
166	M	ID, speech and language delay, cryptorchidism, hirsutism, facial dysmorphism	*ARID1B* c.6700_6701del, p.(Leu2234Glyfs*7)	het; dn	NM_020732.3	P	Coffin-Siris syndrome 1, AD [135900]
176	M	Short stature, pseudomuscular build	*FBN1* c.5284G > A, p.(Gly1762Ser)	het; unk	NM_000138.5	P	Acromicric dysplasia, AD [102370]
243	F	Obesity	*MC4R* c.240C > A, p.(Tyr80*)	het; unk	NM_005912.2	P	Obesity, AD [618406]
251	M	Bone fractures, blue sclerae	*COL1A1* c.1126_1127del, p.(Pro376Trpfs*15) (novel)	het; unk	NM_000088.3	P	Osteogenesis imperfecta type I, AD [166200]
303	F	Neonatal seizures	*KCNQ2* c.620G > A, p.(Arg207Gln)	het; unk	NM_172107.2	P	Benign familial neonatal seizures 1, AD [121200]
307	M	PDA, PFO, hypospadias, cryptorchidism, short stature, facial dysmorphism, hemangioma	*BRAF* c.1741A > G, p.(Asn581Asp)	het; unk	NM_004333.4	LP	Cardiofaciocutaneous syndrome, AD [115150]
349	F	Myasthenic syndrome	*CHAT* c.1165 T > C, p.(Cys389Arg) (novel) *CHAT* c.1493C > T, p.(Ser498Leu)	het; pathet; mat	NM_020549.5	VUS; LP	Presynaptic congenital myasthenic syndrome 6, AR [254210]
395	M	ID, short stature, facial dysmorphism	*KMT2A* c.6665dup, p.(Tyr2222*) (novel)	het; dn	NM_001197104.1	P	Wiedemann-Steiner syndrome, AD [605130]
436	M	ID, DD, hypotonia, vision problems, unilateral hearing loss	*GNB1* c.233A > G, p.(Lys78Arg)	het; dn	NM_002074.4	LP	Autosomal dominant mental retardation 42, AD [616973]
458	M	Short stature, scoliosis, carpal synostosis	*FLNB* c.7029 T > G, p.(Tyr2343*)	hmz, unk	NM_001457.3	P	Spondylocarpotarsal synostosis syndrome, AR [272460]

TABLE 2 (Continued)

No.	Sex	Phenotype	Variant	Zygosity; inheritance	Transcript	CI	Associated condition, inheritance pattern [MIM number]
464	F	ID, neonatal diabetes, annular pancreas, duodenal malrotation	*ABCC8* c.638 T > C, p.(Leu213Pro)	het; unk	NM_001287174.1	LP	Permanent neonatal diabetes mellitus 3, AD [618857]
466	F	Excess skin folds neck, pulmonary artery stenosis, low-set ears	*LZTR1* c.848G > A, p.(Arg283Gln)	het; unk	NM_006767.4	LP	Noonan syndrome 10, AD [616564]
507	F	Hemihypertrophy	*PIK3CA* c.1133G > A, p.(Cys378Tyr)	somatic mosaicism	NM_006218.2	P	Low-level PIK3CA mosaicism associated with hemihypertrophy
511	F	Long QT syndrome	*KCNH2* c.2453C > T, p.(Ser818Leu)	het; pat	NM_000238.3	P	Long QT syndrome 2, AD [613688]
525	M	ASD, cryptorchidism, short stature, facial dysmorphism	*PTPN11* c.417G > C, p.(Glu139Asp)	het; unk	NM_002834.4	P	Noonan syndrome 1, AD [163950]
567	F	Seizures	*SCN1A* c.2134C > T, p.(Arg712*)	het; unk	NM_001165963.1	P	Generalized epilepsy with febrile seizures plus (GEFS+) type 2, AD [604403]
568	M	Seizures	*NPRL2* c.883C > T, p.(Arg295*)	het; unk	NM_006545.4	P	Familial focal epilepsy with variable foci 2, AD [617116]
574	M	Seizures, cortical tubers on brain MRI	*TSC1* c.2509_2512del, p.(Asn837Valfs*11)	het; unk	NM_000368.4	P	Tuberous sclerosis 1, AD [191100]
621	F	Focal segmental glomerulosclerosis	*NPHS2* c.686G > A, p.(Arg229Gln)*NPHS2* c.851C > T, p.(Ala284Val)	het; unkhet; unk	NM_014625.3	P; P	Nephrotic syndrome type 2, AR [600995]
Diagnostic test: single gene analysis							
15	M	Multiple café au lait spots	*NF1* c.4563delT, p.(Ala1523Hisfs*30) (novel)	het; unk	NM_000267.1	P	Neurofibromatosis type 1, AD [162200]
40	M	ID, tall stature, macrocephaly, PDA, facial dysmorphism	*NSD1* c.6049C > T, p.(Arg2017Trp)	het; unk	NM_022455.3	P	Sotos syndrome, AD [117550]
46	M	Hypotonia, loss of motor skills, areflexia	*SMN1* c.835-?_*262 +?del	hmz; unk	NM_000344.3	P	Spinal muscular atrophy type I, AR [253300]
66	F	Short stature, short arms and legs, macrocephaly	*FGFR3* c.1620C > A, p.(Asn540Lys)	het; unk	NM_000142.4	P	Hypochondroplasia, AD [146000]
69[e]	F	Insensitivity to pain	*SCN9A* c.5085_5091dup, p.(Asn1698Tyrfs*3) (novel[c])*SCN9A* c.688 + 131_901 + 2760del, p.(Gly230_Lys301delinsGlu) (novel[c])	het; mathet; pat	NM_002977.3	P; P	Congenital insensitivity to pain, AR [243000]
80	F	Developmental regression, growth retardation	*MECP2* c.91del, p.(Val31*) (novel)	het; unk	NM_004992.3	P	Rett syndrome, XLR [312750]
106	M	ID, microcephaly, hypospadias, feeding difficulties, facial dysmorphism	*NIPBL* c.5778_5808 + 2dup, p.(Val1936_Val1937ins11) (novel)	het; unk	NM_133433.3	P	Cornelia de Lange syndrome 1, AD [122470]
114	F	DD, macrocephaly, facial dysmorphism	*PTEN* c.1003C > T, p.(Arg335*)	het; unk	NM_000314.4	P	Cowden syndrome, AD [158350]
150[f]	F	Hypertension, brachydactyly	*PDE3A* c.1333_1335del, p.(Thr445del) (novel[c])	het; mat	NM_000921.4	P	Hypertension and brachydactyly syndrome, AD [112410]
162	M	Macrocephaly, facial dysmorphism, deep plantar creases	*FGFR2* c.799 T > C, p.(Ser267Pro)	het; unk	NM_000141.4	P	Crouzon syndrome, AD [123500]

(Continues)

TABLE 2 (Continued)

No.	Sex	Phenotype	Variant	Zygosity; inheritance	Transcript	Cl	Associated condition, inheritance pattern [MIM number]
178	F	Seizures, cortical tubers on brain MRI	*TSC2* c.1443 + 1G > A (novel)	het; unk	NM_000548.3	P	Tuberous sclerosis 2, AD [613254]
244	M	DD, behavioral problems, facial dysmorphism	*NSD1* c.6152-14G > A (novel)	het; dn	NM_022455.3	P	Sotos syndrome, AD [117550]
263[g]	M	Lung hypoplasia, enlarged kidneys	*PKHD1* c.5485C > T, p.(Gln1829*)*PKHD1* c.11284C > A, p.(Pro3762Thr)	het; mathet; pat	NM_138694.3	P; LP	Polycystic kidney disease 4, AR [263200]
294	F	Short stature, short limbs, macrocephaly	*FGFR3* c.1138G > A, p.(Gly380Arg)	het; unk	NM_000142.4	P	Achondroplasia, AD [100800]
302	F	Seizures, cortical and subcortical tubers on brain MRI, hypopigmented macules	*TSC2* c.4183C > T, p.(Gln1395*)	het; unk	NM_000548.3	P	Tuberous sclerosis 2, AD [613254]
304[h]	M	Camptodactyly of the fingers, bowed lower limbs, club feet, facial dysmorphism	*LIFR* c.1252C > T, p.(Arg418*)*LIFR* c.1789C > T, p.(Arg597*)	het; unkhet; unk	NM_002310.6	P; P	Stuve-Wiedemann syndrome, AR [601559]
338	F	Tall stature, increased arm span-to-height ratio, myopia	*FBN1* c.5839 T > A, p.(Cys1947Ser) (novel)	het; unk	NM_000138.3	P	Marfan syndrome, AD [154700]
411	M	Capillary malformations	*RASA1* c.655del, p.(Ser219Hisfs*6) (novel)	het; unk	NM_002890.2	P	Capillary malformation-arteriovenous malformation 1, AD [608354]
439	F	Tall stature, increased arm span-to-height ratio	*FBN1* c.1496G > C, p.(Cys499Ser)	het; unk	NM_000138.3	P	Marfan syndrome, AD [154700]
488	F	DD, multiple café au lait spots	*NF1* c.4267A > G, p.(Lys1423Glu)	het; unk	NM_000267.3	P	Neurofibromatosis type 1, AD [162200]
Diagnostic test: trio ES							
16[i]	F	ID, short stature, GH deficiency, congenital hypothyroidism, congenital cataract	*RNPC3* c.259C > T, p.(Gln87*) (novel[c]) *RNPC3* c.443G > C, p.(Gly148Ala) (novel[c])	het; mathet; pat	NM_017619.3	P; LP[j]	Pituitary hormone deficiency, combined or isolated, 7 [618160]

Note: Only patients for whom informed consent was obtained are included in this table.

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ASD, atrial septal defect; Cl., classification; dn, de novo; ES, exome sequencing; F, female; GH, growth hormone; hem, hemizygous; het, heterozygous; hmz, homozygous; ID, intellectual disability; LP, likely pathogenic; M, male; mat, maternal; NGS, next-generation sequencing; P, pathogenic; pat, paternal; PDA, patent ductus arteriosus; PFO, patent foramen ovale; unk, unknown; VUS, variant of unknown significance.

[a]Previously published (Verberne, Dalen Meurs, et al., 2020; Verberne, Faries, et al., 2020; Verberne, Manshande, et al., 2020).

[b]Previously published (Fountain et al., 2019). Affected twin with the same molecular diagnosis not included in this cohort.

[c]Novel variant, but genetic details regarding this individuals have been previously published.

[d]Variant classification different from original report. USP7 c.3202 + 1G > T had been reported as VUS but reclassified as likely pathogenic after more patients with variants in this gene were identified and the phenotype had been described (criteria according to Richards et al., 2015: PVS1, PS2, PM2).

[e]Previously published (Stunnenberg et al., 2021).

[f]Previously published (Renkema et al., 2018).

[g]Genetic testing was performed in both parents based on the results of the autopsy (clinical diagnosis of autosomal recessive polycystic kidney disease).

[h]Previously published (Van De Maele et al., 2019).

[i]Previously published (Verberne, Dalen Meurs, et al., 2020; Verberne, Faries, et al., 2020; Verberne, Manshande, et al., 2020). Affected siblings with the same molecular diagnosis not included in this cohort.

[j]Variant classification different from original report. The *RNPC3* c.443G > C p.(Gly148Ala) variant was reclassified from VUS to likely pathogenic after segregation analysis in siblings (criteria according to Richards et al., 2015: PM2, PM3, PP1, PP3).

TABLE 3 Molecular diagnoses: Copy number variants

No.	Sex	Phenotype	Variant(s)	Class	Associated condition
35	M	ID, speech and language delay, *pectus excavatum*, widely spaced eyes	arr[GRCh37] 15q11.2 (22750305_23272733)x1	P (sl)	15q11.2 deletion syndrome
45	F	DD, hypotonia, clubfoot, facial dysmorphism	arr[GRCh37] 19p13.3 (275925_2286201)x3 dn	P	19p13.3 duplication (~2 Mb)
83	M	ID, seizures, microcephaly, clinodactyly	arr[GRCh37] 15q11.2q13.2 (22299434_30657952) x3,15q13.2q13.3 (30936285_32514341)x3	P; P (sl)	15q11.2q13.2 duplication/triplication (~8.4 Mb; overlapping PWS/AS deletion syndrome region) and 15q13.2q13.3 duplication (~1.6 Mb; including *CHRNA7*)
84	M	ID, hirsutism, ptosis, downslanted palpebral fissures, high forehead, uplifted earlobe	arr[GRCh37] 19q13.42q13.43 (55447595_59097160) x3,22q11.1q11.21 (16197021_20733495)x3	P; P	19q13.42q13.43 terminal duplication (~3.6 Mb) and 22q11.1q11.21 duplication (~4.5 Mb; overlapping with cat eye syndrome region and part of DiGeorge syndrome critical region)
104	F	Short stature, failure to thrive, Dandy-Walker variant, patent foramen ovale	arr[GRCh37] 17q12 (34815551_36450598)x3 dn	P	17q12 duplication syndrome
122[a]	F	ID, facial dysmorphism	arr[GRCh37] 6p22.3 (15374392_15405436)x1 dn	LP	6p22.3 deletion (~31 kb; including exon 2 of *JARID2*)
128	M	DD, cryptorchidism, hypotonia, obesity, partial empty sella	arr[GRCh37] 15q11.2q13.1 (23656946_28535266)x1 dnMS-MLPA: deletion of paternal 15q11q13 allele	P	Prader-Willi syndrome
129	M	Agenesis of the corpus callosum, hypotonia, facial dysmorphism	arr[GRCh37] 8p23.3p23.1 (164984_7007415)x1,8p23.1p11.1 (12494265_43674370) x3,8q23.3q24.3 (115320834_146293414)x3 dn	P	Suggestive of 8p inverted duplication/ deletion syndrome
132	M	DD, microcephaly, lissencephaly, agenesis of the corpus callosum, short stature, facial dysmorphism	arr[GRCh37] 10q23.31q24.1 (91959144_99204791)x1 dn	P	10q23.31q24.1 deletion (~7.2 Mb; including *KIF11* and *LGI1*)
154	M	Supravalvular aortic stenosis, supravalvular and peripheral pulmonary stenosis	arr[GRCh37] 7q11.23 (72994476_74000679)x1	P	7q11.23 deletion (~1.0 Mb; including *ELN*)
163	F	ID, hypotonia, severe scoliosis, facial dysmorphism	arr[GRCh37] 10p14p12.33 (8926204_18332112)x1	P	10p14p12.33 deletion (~9.4 Mb)
169	M	DD, hypotonia, facial dysmorphism	arr[GRCh37] 14q32.32q32.33 (103306215_106199579)x1 dn	P	14q32.32q32.33 deletion (~2.9 Mb)
174	M	ID, facial dysmorphism	arr[GRCh37] 3q24q26.1 (144955389_161517861)x1	P	3q24q26.1 deletion (~16.5 Mb)
249	F	Lissencephaly, facial dysmorphism	arr[GRCh37] 17p13.3 (2540998_2563261)x1	P	17p13.3 deletion (~22 kb; including exon 2 of *PAFAH1B1*)
252	M	DD, macrocephaly, facial dysmorphism	arr[GRCh37] 16p12.2 (21839340_22409463)x1	P	16p12.2 deletion syndrome
271	M	DD, microcephaly, cryptorchism, synophrys, hirsutism	arr[GRCh37] 6q25.3q26 (156833278_161216608)x1	P	6q25.3q26 deletion (~4.4 Mb; including *ARID1B*)
300	F	Speech and language delay, short stature, obesity, facial dysmorphism	arr[GRCh37] 9q31.1q31.3 (105904199_114366248)x1	P	9q31 deletion syndrome
310	M	DD, VSD, facial dysmorphism	arr[GRCh37] 1q21.1q21.2 (146089268_149376652)x1 dn	P	1q21.1 deletion syndrome
340	M	DD, microcephaly, failure to thrive, facial dysmorphism	arr[GRCh37] 7q21.13q21.3 (89613897-94411523)x1 dn	P	7q21.13q21.3 deletion (~4.8 Mb)
352	F	Facial dysmorphism	arr[GRCh37] 9p24.3p22.3 (203861_16031471)x1	P	9p24.3p22.3 deletion (~16 Mb)

(Continues)

TABLE 3 (Continued)

No.	Sex	Phenotype	Variant(s)	Class	Associated condition
375	F	Mayer-Rokitansky-Küster-Hauser syndrome, obesity	arr[GRCh37] 16p11.2 (28825605_29043450)x1	P	16p11.2 microdeletion syndrome
380	F	Short stature, obesity, irregular menstruation	arr[GRCh37] 15q11.2 (25068609_25084319)x1	P	15q11.2 deletion (~15.7 kb; including exon 1–3 of *SNRPN*)
433	M	DD, hypotonia, peripheral pulmonary stenosis, microcephaly, facial dysmorphism	arr[GRCh37] 7q11.23 (72718277_74142190)x1,16p13.11 (15058820_16330672)x3	P; P (sl)	Williams syndrome; 16p13.11 deletion syndrome
494	F	Club feet, agenesis of the corpus callosum, hydronephrosis, hypotonia, pulmonary hypertension, facial dysmorphism	arr[GRCh37] 3q11.1q21.3 (93878600_126099226)x1	P	3q11.1q21.3 deletion (~32 Mb)
510	F	Scimitar syndrome, facial dysmorphism	arr[GRCh37] 6q27 (166502703_170919470)x1	P	6q27 deletion (~4.4 Mb)
518	F	PKD, subcortical tubers, hypertrophic cardiomyopathy, hypopigmentation	arr[GRCh37] 16p13.3 (2106894_2131457)x1 dn	P	16p13.3 deletion (~25 kb; including several exons of *TSC2* and possibly *PKD1*)
538	M	Cleft lip and palate, mild ID, tubular nose, low-set ears, long fingers	46,XY,del(21)(q22.3).arr[GRCh37] 21q22.3(43229099_46312018) x1,21q22.3(46337565_48100155) x1 dn	P; P	21q22.3 deletion (~3.1 Mb) and 21q22.3 terminal deletion (~1.8 Mb)
539	M	DD, facial dysmorphism	46,XY.nuc ish 22q13.2 (RP11-101F24x3).arr[GRCh37] 22q13.1q13.2 (39606071_43462451)x3 dn	P	22q13.1q13.2 duplication (~3.9 Mb)
570	F	DD, seizures, autism	arr[GRCh37] 15q11.2 (22669052-23217514)x3	P (sl)	15q11.2 duplication syndrome
571	M	Seizures, microcephaly	arr[GRCh37] 20q13.33 (61987414_62147896)x1	P	20q13.33 deletion (~160 kb; including *CHRNA4*, *KCNQ2* and *EEF1A2*)
616	M	Cleft lip and palate, hearing loss, tubular nose, long fingers	arr[GRCh37] 22q11.21q11.22 (21808750_22955072)x1 dn	P	Distal 22q11.2 deletion syndrome

Note: Only patients for whom informed consent was obtained are included in this table.
Abbreviations: Class, classification; DD, developmental delay; dn, de novo; ID, intellectual disability; LP, likely pathogenic; MS-MLPA, methylation-specific multiplex ligation-dependent probe amplification; P, pathogenic; PKD, polycystic kidney disease; sl, susceptibility locus; VSD, ventricular septal defect.
[a]Previously published (Verberne et al., 2021).

contacted, we included only general data about the diagnosis (type, inheritance pattern, etc.) and we did not include these patients in Tables 2–4.

2.3 | Data collection and analysis

Clinical data and results of genetic testing were abstracted from the medical records. All variants reported as a variant of unknown significance were reviewed and, if applicable, reclassified according to current guidelines (Association for Clinical Cytogenetics, 2007; Richards et al., 2015; Riggs et al., 2020). We considered a diagnosis to be established if a likely pathogenic or pathogenic variant was identified that explained the phenotype. Diagnostic yield was determined for all patients that received genetic testing. In addition, diagnostic yield per type of genetic test and per reason for referral was calculated. We only calculated diagnostic yield for subgroups with+ ++ $n > 10$. VUS rate was calculated per type of genetic test. To assess the clinical utility of the diagnosis, the referring physicians were asked to report if the diagnosis had led to changes in clinical management and if so, what the changes were. The answers were subsequently categorized into different subgroups. The answer 'no further diagnostics' was not included as a clinical consequence, as this would apply to all patients who received a genetic diagnosis. In addition, "special education" was excluded since this is also available without a genetic diagnosis. All descriptive statistics were performed using SPSS version 26.0 and Excel.

3 | RESULTS

3.1 | Patient demographics

A total of 331 patients were included in this study. The median age at the time of the first genetic consultation was 3.95 years (range 0–18.7), excluding the 9 children that deceased before they could be

TABLE 4 Molecular diagnoses: Other variant types

No.	Sex	Phenotype	Variant	Associated condition
Aneuploidies				
109	F	Severe midline defect	47,XX,+13.arr(13)x3	Patau syndrome
165	F	ID, facial dysmorphism	arr(21)x3	Down syndrome
218	F	ID, hypotonia, facial dysmorphism	arr(21)x3	Down syndrome
278	F	DD, scoliosis, facial dysmorphism	arr(13)x3[0.15]	Mosaic trisomy 13
401	M	Speech and language delay, tall stature	arr(X)x1,(Y)x2	XYY syndrome
544	M	PDA, facial dysmorphism	arr(X)x2,(Y)x1	Klinefelter syndrome
550	F	PDA, facial dysmorphism, sandal gap	47,XX,+21.arr(21)x3	Down syndrome
610	F	Hypotonia, facial dysmorphism, sandal gap	arr(21)x3	Down syndrome
Derivative chromosomes				
7	F	Hypotonia, short stature, hypopigmentation, sparse hair, frontal bossing, thick eyebrows, widely spaced eyes	nuc ish(ETV6x4,RUNX1x2)[24/100]	Pallister-Killian syndrome
115[a]	F	DD, hypotonia, microcephaly, facial dysmorphism	mos 47,XX,+der(1)(::q10- > q23.3::)[4]/46,XX[12].arr[GRCh37] 1q21.1q23.3 (144854574_162843606)x2 ~3	Mosaic trisomy 1q10q23.3
161	F	Agenesis of the corpus callosum, HLHS, truncus arteriosus, TAPVD, hirsutism	46,XX,inv(12)(p?11.2q?14),der(13)t(8;13)(p11.1;p11.1).arr[GRCh37] 8p23.3p11.1 (164984_43674370)x3	Trisomy 8p
Aberrant methylation				
324	F	Hemihyperplasia	Hypomethylation *KCNQ1OT1* (*LIT1*)	Isolated hemihyperplasia
447	M	Short stature, relative macrocephaly, frontal bossing, clinodactyly of the 5th fingers	Hypomethylation *H19*	Silver-Russell syndrome
471	M	Omphalocele, ear lobe creases	Hypomethylation *KCNQ1OT1* (*LIT1*)	Beckwith-Wiedemann syndrome
Repeat expansions				
48	M	ID, long face, hand flapping	*FMR1*: CGG repeats in premutation (n = ~100 and n = ~200) and mutation range (n > 200)	Fragile X syndrome
492	M	ID, DD, epilepsy, hand biting, large testes	*FMR1*: CGG repeats in premutation (n = ~78 and n = ~142) and mutation range (n > 200)	Fragile X syndrome
UPD				
449	M	SGA, short stature, relative macrocephaly, facial dysmorphism	arr[GRCh37] 7p15.3q21.11 (24803592_81535350)x2 hmz,7q34q36.3 (138746752_159126310)x2 hmz	UPD7, clinically suggestive of Silver-Russell syndrome (maternal UPD)
Multiple variant types				
88	M	Bilateral radial aplasia, bilateral ulnar hypoplasia, thrombocytopenia	arr[GRCh37] 1.q21.1 (145395440_145762959) (paternal) *RBM8A* c.-21G > A, p.(?), hemizygous (maternal)	Thrombocytopenia-absent radius (TAR) syndrome

Note: Only patients for whom informed consent was obtained are included in this table.
Abbreviations: DD, developmental delay; HLHS, hypoplastic left heart syndrome; ID, intellectual disability; PDA, patent ductus arteriosus; SGA, small for gestational age; TAPVD, total anomalous pulmonary venous drainage; UPD, uniparental disomy.
[a]Previously published (Lo-A-Njoe et al., 2016).

seen by the clinical geneticist. The most common reasons for referral were developmental delay (DD) and/or intellectual disability (ID) (39%), with or without other anomalies, and congenital anomalies (24%). Other reasons for referral to the visiting clinical geneticist included short stature (8%), suspected connective tissue disorder (5%), obesity (5%), and seizures (4%).

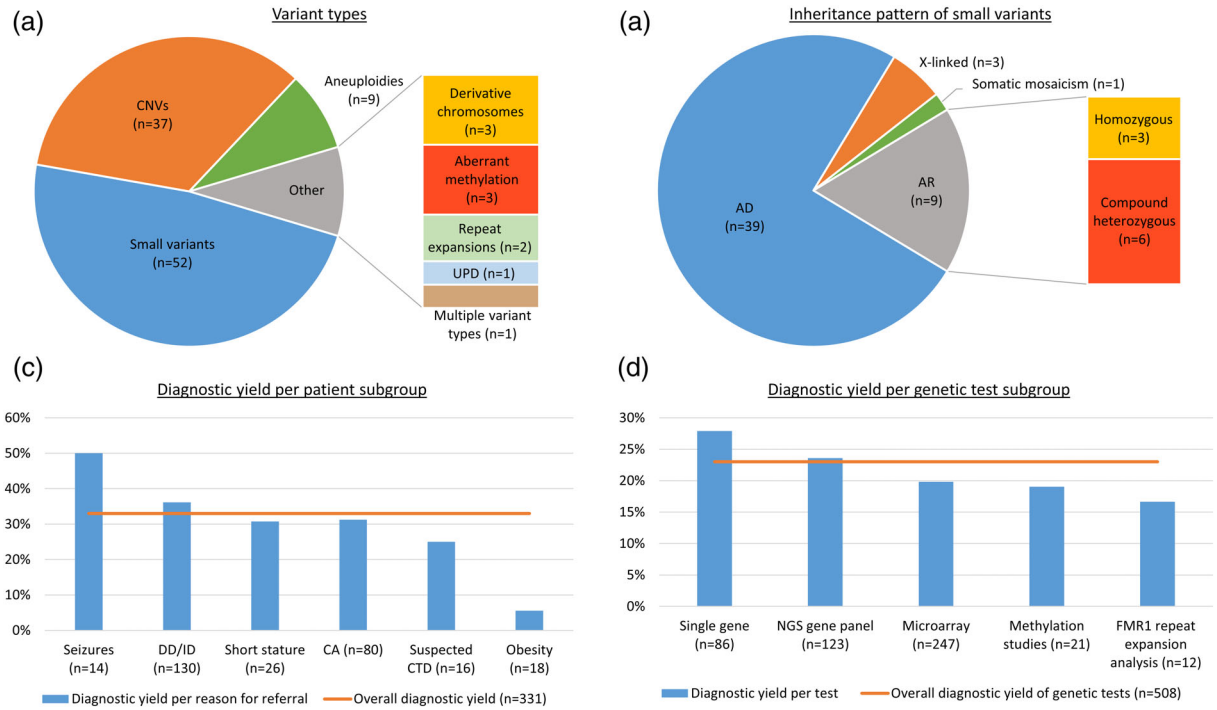

FIGURE 1 Molecular diagnostic results. (a) Variant types. (b) Mode of inheritance in patients with small variants (single nucleotide variants or small insertions and/or deletions). (c) Molecular diagnostic yield per primary reason for referral (reason for referral only included if $n > 10$). (d) Molecular diagnostic yield per type of genetic test (genetic test only included if $n > 10$). AD, autosomal dominant; AR, autosomal recessive; CA, congenital anomalies; CNVs, copy number variants; CTD, connective tissue disorder; DD/ID, developmental delay and/or intellectual disability (with or without other anomalies); NGS, next-generation sequencing; NGS, next-generation sequencing; UPD, uniparental disomy

3.2 | Genetic testing

A total of 508 genetic tests were performed (average of 1.5 tests per patient). One genetic test was performed in 60% of patients, two genetic tests in 29%, three genetic tests in 8%, four genetic tests in 3%, and five genetic tests in <1%. Microarray was the most frequently requested test ($n = 247$; 49%), followed by (NGS) gene panels (targeted or exome based) ($n = 123$; 24%), single-gene analysis ($n = 86$; 17%), methylation studies ($n = 21$; 4%), *FMR1* repeat expansion analysis ($n = 12$; 2%), and karyotyping ($n = 10$; 2%). Trio ES, fluorescence in situ hybridization (FISH), and X-exome each comprised <1% of the total amount of genetic tests. Previous genetic testing had been performed in only 11 (3%) of the patients, with normal or inconclusive results.

3.3 | Diagnostic yield

A molecularly confirmed diagnosis was established in 108 patients (33%). In 52 patients (48%) single nucleotide variants (SNVs) or small insertions and/or deletions (indels) were detected. Copy number variants (CNVs) were identified in 37 patients (34%). Other variant types included aneuploidies ($n = 9$; 8%), derivative chromosomes ($n = 3$; 3%), aberrant methylation ($n = 3$; 3%), repeat expansions (2; 2%), loss of heterozygosity consistent with uniparental disomy (UPD) ($n = 1$; 1%), and multiple variant types ($n = 1$; 1%) (Figure 1a). Of the 52 patients with small variants (SNVs/indels), 39 (75%) had a variant associated with an autosomal dominant disorder: six of these variants were de novo, two were inherited from an affected parent, and for 31 variants inheritance was unknown. Small variants associated with autosomal recessive disorders were identified in nine patients (17%): three patients with homozygous variants and six with compound heterozygous variants (Figure 1b). The molecular diagnostic results and associated conditions of patients for whom informed consent was obtained are shown in Table 2-4. Recurrent molecular diagnoses included: Down syndrome ($n = 4$), Marfan syndrome ($n = 2$), Sotos syndrome ($n = 2$), Tuberous Sclerosis type 2 ($n = 2$), Neurofibromatosis type 1 ($n = 2$), and Fragile X syndrome ($n = 2$). Patients with the same diagnosis were not related. No recurrent variants were detected in this cohort.

Molecular diagnostic yield was highest in patients referred for seizures (7/14; 50%) and in patients referred because of DD/ID (47/130; 36%). The lowest molecular diagnostic yield was found in patients that received genetic testing for obesity (1/18; 6%) (Figure 1C). The diagnostic yield per type of genetic test was highest for single gene testing (24/86; 28%), followed by NGS gene panels (29/123; 24%) and microarray (49/247; 20%) (Figure 1D).

In addition to the 108 molecular diagnoses, 7 clinical diagnoses were established in this cohort. These included amniotic band syndrome, fetal methotrexate syndrome (Verberne, Dalen Meurs,

et al., 2020; Verberne, Faries, et al., 2020; Verberne, Manshande, et al., 2020), VACTERL association, and oculo-auriculo-vertebral spectrum (OAVS), for which there is no known genetic cause. For the other clinical diagnoses (Apert syndrome, Tuberous Sclerosis, and oculoectodermal syndrome [OES]), genetic testing was negative or not yet performed.

3.4 | Variants of unknown significance and incidental findings

One or more VUS were identified in 44/247 (18%) microarrays that were performed, in 34/123 (28%) NGS gene panels, in 1/86 (1%) single-gene tests, and in 2/3 (67%) trio ES (excluding heterozygous VUS in genes associated with autosomal recessive conditions). In total, 110 VUS were identified in 78 patients (24% of the cohort), including 59 CNVs and 51 small variants. Segregation analysis was performed for 49 variants and resulted in the reclassification of 23/33 (70%) CNVs as rare familial polymorphisms and 5/16 (31%) small variants as likely benign. Three VUS were identified more than once: a ~122 kb deletion in 5p12 that was identified in five individuals and a ~393 kb 9q22.1 duplication coupled with a ~538 kb 9q22.31 duplication in four individuals. Two of the individuals with a 5p12 deletion were halfsiblings, but all other individuals were apparently unrelated. There was no common phenotype between individuals with the same VUS. Segregation analysis was performed for three individuals with the 5p12 deletion and one individual with the 9q22.1 and 9q22.31 duplications: these VUS were all inherited from a healthy parent.

Finally, two incidental findings were detected by microarray, both susceptibility loci for neurodevelopmental disorders that did not explain the phenotype for which the patient was referred.

3.5 | Impact on clinical management

Information on the clinical consequences of the molecularly confirmed diagnosis was available for 88 patients (81%). The genetic diagnosis had an impact on clinical management in 46 (52%) of these patients. The reported clinical consequences are summarized in Table 5. The most frequently reported consequences were referrals to health professionals. These were mainly referrals to other medical specialists for screening for associated risks and/or therapeutic advice, but also included referrals to a physiotherapist, speech therapist, and dietician. Changes in therapy or medication included, for example, a change in anti-epileptic medication in patient 567 with GEFS+ and patient 574 with Tuberous Sclerosis and indication for growth hormone therapy in two patients with Silver-Russel syndrome, but also discontinuing corticosteroid treatment in patient 621 with steroid-resistant nephrotic syndrome. Standardized follow-up care according to the protocol of a specific disorder, such as Down syndrome, Marfan syndrome, and Noonan syndrome, was started in nine individuals. Additional diagnostics were reported in five patients and include, for example, magnetic resonance imaging (MRI) in patient 131 with hypomyelinating leukodystrophy 8 and in patient 411 with capillary malformation-arteriovenous malformation 1. In some patients, the genetic diagnosis guided clinical decision making. For instance, the decision was made to continue anti-epileptic medication in patient 571 after he was diagnosed with a 20q13.33 deletion encompassing several epilepsy-associated genes. Consequences for surveillance include tumor screening in patient 114 with Cowden syndrome and patient 471 with Beckwith-Wiedemann syndrome, but also discontinuing tumor screening in patient 324 with isolated hemihyperplasia related to *KCNQ1OT1* hypomethylation. Finally, other examples of clinical consequences include the referral of patient 574 with Tuberous Sclerosis to an expertise center in the Netherlands, but also prevention of an overseas referral to Colombia for diagnostic work-up in patient 567 with GEFS+.

TABLE 5 Impact on clinical management of molecularly confirmed diagnosis

Consequence in management	*n*
Referral to health professional(s)	13
Change in therapy/medication	11
Standardized follow-up care	9
Additional diagnostics	5
Guided clinical decision making	4
Change in surveillance	3
Treatment limitations	3
(Avoid) overseas referral	2
Tailored advice	2
Access to support services	2

Note: Total does not add up to 46, as there were several different clinical consequences for some patients.

4 | DISCUSSION

In this retrospective cohort study, we demonstrate that our genetic service with a visiting clinical geneticist in the Dutch Caribbean results in a molecularly confirmed diagnosis in 33% of patients with a suspected genetic disorder. Since ES is not (yet) part of standard care in the Dutch Caribbean and financial restrictions prompt a more targeted and proband-only approach, we believe this is a reasonably high diagnostic yield. In addition, in 52% of patients, the established diagnosis had an impact on clinical management.

Over the past few years, several other efforts have been made to improve access to genetic services in the Caribbean. Recently, Sobering et al. (2020) described their experiences with offering genetic services with a visiting clinical geneticist on several resource-limited Caribbean islands. They present the results of genetic testing in more than 100 individuals with suspected genetic disorders and report a diagnostic yield of exome sequencing of ~50%. Another study reports on an international telemedicine program in the Dominican Republic, through which a genetic molecular diagnosis was obtained for 39/57

(68%) individuals that received genetic testing, mostly through exome sequencing (Mena et al., 2020). Finally, Scantlebury et al. (2021) describe their experience with performing ES for the first time in five patients on the Eastern Caribbean island of Barbados, identifying a diagnostic pathogenic variant in three patients and a VUS in one patient. Studies in other resource-limited areas show similar promising results, with a diagnostic yield ranging from 29% for proband-only exome sequencing of known Mendelian disease genes in a Chinese study (Hu et al., 2018), to a yield of 68% in a Mexican study on clinical genome sequencing (Scocchia et al., 2019). Moreover, studies that also investigated clinical consequences of the genetic diagnosis report an impact on clinical management in 45–69% of patients (Hu et al., 2018; Mena et al., 2020; Scocchia et al., 2019). Thus, genetic services can significantly contribute to healthcare even in lower resource settings.

In the present study, we describe the outcomes of genetic testing in the largest Caribbean cohort so far. A possible limitation of our study is that selection bias due to financial restrictions could explain the relatively high diagnostic yield, as patients with a high suspicion of a genetic disorder were more likely to receive genetic testing. On the contrary, the percentage of patients with a genetic disorder in our cohort is probably an underestimation, as more extensive genetic testing such as trio ES was not performed in the majority of patients. In addition, 12 patients with a diagnosis were excluded from this study as informed consent was not provided, resulting in a slight underestimation of the diagnostic yield. The main strength of our study is the retrospective design, which allows evaluation of the outcomes of the actual decision making process in clinical practice. In addition, although the consultations and counseling are currently provided as a service from the Amsterdam UMC Human Genetics Department, all residents of the Dutch Caribbean (except for St. Maarten) are entitled to basic health insurance that should cover the costs of genetic testing. This increases the accessibility and sustainability of our genetic service.

In our cohort, the highest diagnostic yield was achieved in patients with seizures and patients with DD/ID (50% and 37%, respectively). These percentages reflect the combined yield of the different genetic tests that were performed. Diagnostic yield for DD/ID is comparable to previous studies on ES (Srivastava et al., 2019), but diagnostic yield in patients with seizures is high compared to previous reports (Sánchez Fernández et al., 2019; Symonds & McTague, 2020). However, this number may be biased as there were only 14 patients with epilepsy included in our study. The lowest molecular diagnostic yield in our cohort was found for patients with obesity (6%), which is comparable to previous studies (Kleinendorst et al., 2018; Nordang et al., 2017). The diagnostic yield of single-gene testing and NGS gene panels was relatively high in our cohort. This may be explained by the stringent selection of patients in clinical practice due to financial limitations. the diagnostic yield of microarray in our cohort was 20%, which is within the previously reported range of 15%–20% (Miller et al., 2010).

Because the Dutch Caribbean islands have small populations, we expected to find a high rate of recessive disorders. This hypothesis was however not confirmed in our cohort: 9 (17%) of the 52 patients with small variants had an autosomal recessive disorder, of which only 3 patients had a homozygous variant. Nevertheless, autosomal recessive hemoglobinopathies are relatively common in the Dutch Caribbean population (van der Dijs et al., 1992; van Heyningen et al., 2009). These patients are, however, generally not referred to the clinical geneticist and, therefore, not included in our cohort. Furthermore, founder effects have been observed in (small) island populations for autosomal dominant disorders, including in the Dutch Caribbean islands of Bonaire and Curaçao, where the highest worldwide known prevalence of hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease) has been found (Gallione et al., 2000). Although we identified a few recurrent molecular diagnoses in our cohort, we did not detect any recurrent (founder) variants. However, our study was not designed to detect founder variants.

One of the challenges of our proband-only approach was the interpretation of VUS. Ideally, segregation analysis in the family or functional testing is performed to further classify a VUS, but this was often not possible because of financial restrictions. In addition, the Dutch Caribbean population is predominantly of African and Latin-American descent. Although ethnic diversity in genome reference data is increasing, several populations of non-European ancestry, including African and Latin American, are still underrepresented in population-based genomic studies (Landry et al., 2018; Pereira et al., 2021). This may lead to racial/ethnic disparities in VUS rates, with higher proportions of VUS in individuals of non-European ancestry (Caswell-Jin et al., 2018; Kurian et al., 2018; Pottinger et al., 2020). In our cohort, three recurrent VUS were identified: a 5p12 deletion and 9q22.1 and 9q22.31 duplications. We argue that these are likely normal genetic variants in the Dutch Caribbean population. In view of this, our aim for the future is to establish a database of genomic variants for the (Dutch) Caribbean population.

Finally, there are several challenges in the organization and realization of this bi-annual pediatric-genetics clinic. For example, pediatricians have to be very selective in referring patients, as there are generally only two or 3 days of clinic per island. During these days, follow-up visits also have to be scheduled. Moreover, when genetic test results are known, patients may have to wait several weeks or even months before they can speak to the clinical geneticist again. In these instances, telemedicine may be useful to provide additional consultations between the live visits. In addition, telemedicine may provide a good alternative for live visits when travel restrictions because of the coronavirus disease 2019 (COVID-19) pandemic, apply.

In conclusion, we show that despite financial restrictions, a diagnostic yield of 33% can be reached with targeted genetic testing in patients with a high suspicion of a genetic disorder. Moreover, we show that even in this resource-limited setting, the genetic diagnosis had an impact on clinical management in 52% of patients. Our approach with a visiting clinical geneticist may be an example for other countries, in particular other small islands where clinical genetics services are not (yet) available.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

ETHICS APPROVAL STATEMENT

The Medical Ethical Committee of the Amsterdam University Medical Center, location AMC, assessed the study protocol and confirmed that the study was exempt from ethics review according to the Medical Research Involving Human Subjects Act.

AUTHORS CONTRIBUTIONS

EAV and MMvH designed the study. EAV, JMW, and TIdV collected the data. LTvdV, KHvA, AMvdKK, and MA reviewed the results of genetic testing. EAV analyzed the data and drafted the manuscript. EAV, JMW, TIdV, GMEG, SMLAN, MEM, SF, HDV, PP, FAF, IRA, MPW, LRC, PT, EA, MdV, SQN, MT, and MMvH performed the clinical evaluations of the patients. GMEG, MMAMM, and MMvH supervised the project. All authors revised and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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