This information is for health professionals. It is not essential that you read this section.

Subject information	Order Information
Name: John Doe	**Type of Test:** ***myLifeCancer***™
Sex: Male	**Sample Type:** Buccal swab
D.O.B: dd.mm.yyyy	**Internal ID:**xxxx
Age: 18 years old	**Order date:** 27.09.2021
Box ID: arxxxxxxx	**Sample collection date:** 12.08.2021
Payment ID: DNA-xxxxxxxxxx	**Sample arrival date:** 18.08.2021
E-mail: john.doe@email.com	**Date of report: 18.09.2021**

Requested test: *myLifeCancer*™

Consent for the evaluation of **incidental findings** was given by the subject.

Medical summary

- **Family History**: Family history of colorectal cancer (father and uncle).
- **Physical Information**: not provided.
- **Clinical manifestations**: not provided

Summary of the genetic results

Primary Finding

A heterozygous pathogenic variant was identified in the ***APC* gene**. The genetic diagnosis of **autosomal dominant familial adenomatous polyposis type 1** is confirmed.

Incidental Finding

We did not detect any class 1 and 2 variants in the genes for which incidental findings are reported based on the ACMG guidelines.

Recommendation

- Clinical correlation is advised.
- Familiar genetic testing is advised to stablish whether the pathogenic variant ***APC*** variant is inherited in close relatives at risk.
- Genetic counselling is recommended.

Interpretation of primary finding

By Whole Genome Sequencing (WGS), we have identified a heterozygous genetic variant in APC regulator of Wnt signaling pathway (APC) gene**.** The APC gene encodes a multidomain protein that plays a major role in tumor suppression by antagonizing the WNT (see WNT1; OMIM 164820) signaling pathway. Inappropriate activation of this pathway through loss of APC function contributes to cancer progression, as in familial adenomatous polyposis (FAP; OMIM 175100). APC also has a role in cell migration, adhesion, chromosome segregation, spindle assembly, apoptosis, and neuronal differentiation (Hanson and Miller, 2005). The APC protein is an integral part of the beta-catenin (CTNNB1; OMIM 116806) signaling pathway.

Gene/OMIM		***APC*/ 611731**
Genomic coordinate (GRCh38)		Chr5: 112766407
ID Transcript		NM_000038.6
HGVS[1] nomenclature		c.219del
Protein change		p.(Glu74Serfs*4)
Location		Exon 3 of 16
Zygosity		**Heterozygous**
Function		frameshift_variant
Impact		HIGH
ClinVar		Pathogenic
Allele Frequency	*Local Database*	-
	gnomAD[2]	-
In silico Predictors	MetaLR	-
	MetaSVM	-
	DANN	Pathogenic
	Mutation Taster	Disease causing
Clinical significance		**Pathogenic (class 1)**
ACMG[3] Criteria		PVS1 very strong; PM2 strong

[1]HGVS= Human Genome Variation Society; [2]gnomAD= Genome Aggregation Database; [3]ACMG= American College of Medical Genetics and Genomics; Class 1: Pathogenic; Class 2: Likely Pathogenic; Class 3: Variant of uncertain significance (VUS); Class 4: Likely benign; Class 5: Benign.

***APC*;**
c.219del
p.(Glu74Serfs*4)

This sequence change creates a premature translational stop signal (p.Glu74Serfs*4) in the APC gene. It is expected to result in an absent or disrupted protein product. This variant is not present in population databases (gnomAD and internal database no frequency). This variant has not been reported in the literature in individuals with APC-related conditions. Loss-of-function variants in APC are known to be pathogenic (PMID: 17963004, 20685668). This variant is classified as pathogenic (class 1) based on ACMG guidelines.

PVS1: Null variant (nonsense, frameshift, canonical ±1 or 2 splice sites, initiation codon, single or multiexon deletion) in a gene where LOF is a known mechanism of disease.

PM2: Absent from controls (or at extremely low frequency if recessive) in gnomAD.

Disease name/ OMIM	MOI	Genotype	Clinical statement
Familial adenomatous polyposis type 1/ 175100	AD	Heterozygote	Affected

MOI: Mode of inheritance; AD: autosomal dominant, AR: autosomal recessive; XL: X-linked

Familial adenomatous polyposis (FAP)

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited cancer predisposition syndrome caused by heterozygous pathogenic variants in the APC gene located on chromosome 5q22. Affected individuals usually develop hundreds to thousands of adenomatous polyps of the colon and rectum, a small proportion of which will progress to colorectal cancer (CRC) if not surgically treated. A milder form of the disease, attenuated familial adenomatous polyposis (AFAP), also contributed to CRC, presents at a later age with a lower polyp burden (PMID: 1651563, PMID: 28786406) Additionally, extracolonic features may be present.
The prevalence of FAP is 1 in 10000 individuals. About 30% of individuals with FAP have no known family history and represent de novo APC pathogenic variants. FAP has a 100% lifetime risk of colorectal cancer if left untreated. Patients with AFAP have a 70% risk of developing CRC (PMID: 25779305, PMID: 28786406).

Clinical manifestations.

Most patients present with nonspecific symptoms including diarrhea, abdominal discomfort, or rectal bleeding. Further visualization using colonoscopy can reveal more than 100 polyps. Some individuals may be asymptomatic and present with colorectal cancer during screening colonoscopy. On physical examination, congenital hypertrophy of the retinal epithelium with localized pigmented lesions is specific for FAP. The patient usually has no visual complaints. Some patients may present with osteomas of the mandible or skull. Abnormalities in dentition, including impacted teeth, supernumerary teeth, odontomas, and cysts, may be identified on a plain film X-ray. In young children, there may be numerous epidermoid cysts on the face, extremities, and scalp. Some patients may have fibromas on the extremities, back, and trunk (PMID: 28786406, PMID: 28617886). Desmoid tumors, solid connective tissue tumors, develop mostly in abdomen cavity in 10-15% of FAP patients (PMID: 28668823). Gastric polyps are present in approximately 90% of patients with FAP. In some FAP patients, gastric polyps can progress to gastric cancer. Patients with FAP also have increased risk (up to 12%) of thyroid cancer development (PMID: 28786406).
In FAP patients, colonic polyps develop at mean age 16 years (range 7-36 years). The polyps in patients with AFAP usually present later. The mean age of CRC diagnosis in untreated FAP individuals is 39 years (range 34-43 years.

Surveillance and treatment.

Colonoscopy (with or without colonoscopic polypectomy) every 6-12 months starting at age 10-15 years. Colonoscopy must be continued with the same frequency after colectomy. Upper endoscopic (including complete visualization of the ampulla of Vater) starting at age 20–25 year (or earlier if aggressive duodenal adenoma burden or cancer present in family history). Thyroid ultrasound every 2–5 years starting in late teenage years. For further information please consult NCCN Guidelines V1.2021, FAP.
For individuals with FAP, colectomy is recommended as soon as colonic polyps are diagnosed. However, in approximately one third of individuals the colonic polyps are limited in number and periodic colonoscopic polypectomy is sufficient. Absolute indications for colectomy include documented or suspected colorectal cancer or significant symptoms (e.g., obstruction, bleeding). Relative indications for colectomy include presence of multiple adenomas larger than 6 mm that cannot be reasonably managed by endoscopy, a significant increase in adenoma number between surveillance examinations, presence of adenomas with high-grade dysplasia or inability to adequately survey the colon (e.g., due to limited access, or non-compliance with colonoscopy). Several types of colectomies can be considered depending on the clinical circumstances. Endoscopic removal of

duodenal and ampullary adenomas is recommended if polyps exhibit villous change or severe dysplasia, exceed one centimeter in diameter, or cause symptoms. In patients with high-risk lesions that cannot be removed endoscopically gastrectomy should be considered. Osteomas and desmoid tumors also may be surgically removed. Chemoprevention may be considered to facilitate management in select patients. There are no FDA-approved medications for this indication at present. While there are data to suggest that sulindac is the most potent polyp regression medication (NCCN Guidelines V1.2021, FAP).

Clinical trials

Clinical trials are essential for the development of new treatments. When considering a clinical trial, a person should try to gather as much information as they can and then do what they feel is best in their own mind. Those who decide to volunteer may be contributing directly to the understanding of diseases and how to treat them. To get further information about clinical trials for Familial adenomatous polyposis, please visit:
https://clinicaltrials.gov/ct2/results?cond=FAP1&term=&cntry=&state=&city=&dist=
https://www.clinicaltrialsregister.eu/ctr-search/search?query=Familial+adenomatous+polyposis

Technical information- Methods

Library preparation and whole genome sequencing has been performed at Cegat (https:\\www.cegat.de), using TruSeq Nano DNA Throughput Library Prep Kit from Illumina®. The libraries are paired end sequenced on an Illumina platform to yield an average coverage depth of ~30x. Raw sequencing data were transformed into FASTQ format and transferred to Varvis® service (Limbus Medical Technologies GmbH; https://www.limbus-medtec.com/).

Computational and data analysis: Sequence reads of each sample were mapped to the human reference genome (hg38). Varvis® version 1.18 has been used for bioinformatics pipeline, including read alignment, variant calling, annotation, variant filtering and analysis. Genetic variants are described following the Human Genome Variation Society (HGVS) recommendations (www.hgvs.org)

myLifeCancer™ was developed and assessed for accuracy and precision by Arcensus. The design of the virtual panel is property of Arcensus and includes the following 1299 genes related to heart medical conditions:

AAGAB, ABCA5, ABCB11, ABCB4, ABCC6, ABCC8, ABCD1, ABL1, ABL2, ABRAXAS1, ACAN, ACBD5, ACD, ACP5, ACTB, ACTG2, ACVR1, ACVR1B, ACVR2A, ACVRL1, ADA, ADA2, ADAMTS20, ADAMTS3, ADAR, ADGRA2, ADGRB3, ADGRB3, ADGRL3, ADH1B, ADH5, AFAP1, AFAP1L2, AFDN, AFF1, AFF3, AFG3L1P, AFP, AGAP3, AGK, AGPHD1, AHCY, AHCYL1, AIP, AJUBA, AKAP9, AKT1, AKT2, AKT3, ALAD, ALDH2, ALG9, ALK, ALX1, ALX3, ALX4, AMER1, ANAPC1, ANKRD26, ANO1, ANPEP, ANTXR1, ANTXR2, AP2S1, APC, APC2, APH1A, APOBEC3A, APOBEC3C, APOBEC3D, APOBEC3G, APP, APPL1, AR, ARAF, ARHGAP26, ARHGAP35, ARID1A, ARID1B, ARID2, ARID5B, ARMC5, ARNT, ARSA, ASCC1, ASCL1, ASPSCR1, ASS1, ASXL1, ATF1, ATM, ATP2A2, ATP6V1B2, ATP7A, ATP7B, ATR, ATRX, AURKA, AURKB, AURKC, AXIN1, AXIN2, AXL, B2M, B3GALT6, B4GALNT1, B4GALT3, BACH1, BAG4, BAIAP2L1, BAK1, BARD1, BAX, BCAN, BCHE, BCL10, BCL11A, BCL11B, BCL2, BCL2A1, BCL2L1, BCL2L11, BCL2L2, BCL3, BCL6, BCL9, BCOR, BCORL1, BCR, BICC1, BIN1, BIRC2, BIRC3, BIRC5, BLK, BLM, BLNK, BMP2, BMPER, BMPR1A, BMPR1B, BRAF, BRCA1, BRCA2, BRD3, BRD4, BRIP1, BTK, BTRC, BUB1, BUB1B, BUB3, C10orf114, C11orf30, C11orf95, C1S, C2CD3, CA6, CA9, CACNA1S, CALR, CARD11, CARD14, CARMIL2, CARS, CASC15 , CASC5, CASP10, CASP7, CASP8, CASR, CAT, CB274, CBFA2T3, CBFB, CBL, CBLB, CBLC, CC2D2A, CCAR2, CCBE1, CCDC170, CCDC22, CCDC50 , CCDC6, CCDC88A, CCL2, CCM2, CCN2, CCNA1, CCNA2, CCNB1, CCNB2, CCNB3, CCND1, CCND2, CCND3, CCNE1, CCNE2, CCR5, CD19, CD2, CD22, CD247, CD27, CD276, CD28, CD33, CD4, CD44, CD58, CD70, CD74, CD79A, CD79B, CD81, CD96, CDAN1, CDC27, CDC73, CDH1, CDH10, CDH11, CDH2, CDH20, CDH23, CDH3, CDH4, CDH5, CDIN1, CDK1, CDK10, CDK12, CDK2, CDK4, CDK5, CDK6, CDK8, CDK9, CDKN1A, CDKN1B, CDKN1C, CDKN2A, CDKN2B, CDKN2B, CDKN2C, CDON, CDX2, CEACAM1, CEBPA, CEBPE, CEL, CENPA, CEP57, CEP72, CEP85L, CEP89, CHD1, CHD2, CHD4, CHD7, CHEK1, CHEK2, CHIC2, CHRNA3, CHRNA5, CHRNG, CIB1, CIC, CIITA, CIT, CKS1B, CLCN2, CLCN6, CLCNKB, CLDN18, CLIP1, CLIP2, CLTC, CLTCL1, CMPK1, CNTRL, COL11A2, COL18A1, COL1A1, COL2A1, COL4A5, COL4A6, COL6A3, COL7A1, COMT,

CPLANE1, CPLX1, CPOX, CR2, CRACD, CRBN, CREB1, CREB3L1, CREB3L2, CREBBP, CRIPAK, CRKL, CRLF2, CRTC1, CSF1R, CSF3R, CSMD3, CTAG1A, CTAG1B, CTAG2, CTBP1, CTC1, CTCF, CTDNEP1, CTHRC1, CTLA4, CTNNA1, CTNNA2, CTNNA3, CTNNB1, CTPS1, CTSA, CTSC, CUL3, CUX1, CXCL13, CXCR4, CYLD, CYP11B1, CYP11B2, CYP1B1, CYP26C1, CYP2A6, CYP2C19, CYP2D6, DAB2IP, DAXX, DCC, DCLRE1C, DCUN1D1, DDB2, DDIT3, DDR1, DDR2, DDX3X, DDX41, DDX41, DEK, DHCR24, DHCR7, DHH, DHX37, DICER1, DIS3L2, DKC1, DLC1, DLL1, DLL3, DLL4, DLST, DMPK, DNAJB1, DNAJB11, DNAJC21, DNASE1L3, DNM2, DNMT3A, DNTT, DOCK8, DOT1L, DPF2, DPM1, DPYD, DST, DTX1, DUSP22, DUSP4, DUSP6, DVL1, DVL3, DYNC2H1, DYNC2LI1, DZIP1L, EBF1, ECE1, ECM1, EDN1, EDN3, EDNRB, EED, EFL1, EFNA4, EGFR, EGLN1, EGLN2, EGR3, EHBP1, EIF2AK3, EIF2AK4, EIF4A2, EIF4E, ELANE, ELF1, ELF3, ELF4, ELL, ELMO2, EML4, ENG, ENPP1, ENPP3, EP300, EPAS1, EPCAM, EPHA2, EPHA3, EPHA5, EPHA7, EPHB1, EPHB2, EPHB4, EPHB6, EPOR, EPOR, EPPK1, EPS15, ERBB2, ERBB2 (HER2), ERBB3, ERBB4, ERC1, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, ERG, ESCO2, ESR1, ETS1, ETV1, ETV4, ETV6, EVC, EVC2, EWSR1, EXO1, EXT1, EXT2, EXTL3, EYA1, EZH2, F13A1, F13B, F5, FAH, FAM111B, FAM149B1, FAM20C, FAN1, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FAS, FASLG, FAT4, FBXW7, FCHO1, FCN3, FDPS, FERMT1, FERMT3, FGF3, FGF8, FGFR1, FGFR2, FGFR3, FGFR4, FGFRL1, FH, FIBP, FL1 , FLCN, FLI1, FLNA, FLT3, FLT4, FN1, FOXA1, FOXA2, FOXC2, FOXE1, FOXI1, FOXL2, FOXO1, FOXO3, FOXP1, FOXP4, FUNDC2P2, FUZ, FYCO1, FZD2, FZR1, G6PC1, G6PD, GABRD, GALNT12, GANAB, GATA1, GATA2, GATA3, GATA4, GBA, GCDH, GCGR, GCK, GCM2, GDF2, GDF5, GDNF, GFI1, GINS1, GJA1, GJB2, GJB3, GJB4, GJB6, GJC2, GLI1, GLI2, GLI3, GNA11, GNAI3, GNAQ, GNAS, GNB1, GNPTAB, GPC3, GPC4, GPC6, GPR101, GPR143, GREM1, GRM8, GSKIP, GTF2E2, GTF2H5, GUCY1A2, H19, H19-ICR, H3F3C, HABP2, HACE1, HAX1, HBB, HCAR1, HCLS1, HDAC4, HFE, HGF, HIF1A, HIST1H1C, HIST1H2BD, HLA-DQA1, HLA-DQB1, HLF, HMBS, HMMR, HNF1A, HNF1B, HNF4A, HOOK3, HOXB13, HOXD-AS1, HPGD, HRAS, HS2ST1, HSD3B2 , HSP90AA1, HSP90AB1, HSPA9, HSPG2, ICK, ICOS, ICR1, IDH1, IDH2, IFIH1, IFNG, IGF1R, IGF2, IGF2R, IGHM, IGLL1, IKBKB, IKBKE, IKBKG, IKZF1, IKZF3, IL12RB1, IL1B, IL1RN, IL2, IL21R, IL2RG, IL6, IL6R, IL6ST, IL7, IL7R, ING1, ING4, INPP5E, INS, INTU, IRF1, IRF4, IRF5, IRS2, ITGA10, ITGA9, ITGB2, ITGB3, ITK, IVNS1ABP, JAG1, JAK1, JAK2, JAK3, JUN, KANSL1, KARS1, KAT6A, KAT6B, KCNE3, KCNH1, KCNJ10, KCNJ11, KCNN3, KCNQ1, KCNQ1OT1, KDELR2, KDM5C, KDM6A, KDM6B, KDR, KDSR, KEAP1, KIAA0753, KIF11, KIF1B, KIF7, KIT, KITLG, KLF11, KLF6, KLHDC8B, KLLN, KMT2C, KMT2D, KMT2D, KRAS, KRIT1, KRT1, KRT10, KRT14, KRT16, KRT17, KRT5, KRT6A, KRT6B, KRT9, L2HGDH, LAMA3, LAMB3, LAMC2, LAMP1, LAPTM5, LCK, LEMD3, LETM1, LIFR, LIG4, LMNA, LMO1, LMOD1, LNCR4 , LPP, LRBA, LRP1, LRP1B, LRP5, LRRC8A, LRRK2, LRRN2, LTF, LTK, LZTR1, LZTS1, MAD1L1, MAD2L2, MAF, MAFA, MAFB, MAGEA1, MAGI1, MAGT1, MALT1, MAML2, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAP3K7, MAP3K8, MAPK1, MAPK8, MAPK8IP1, MAPRE2, MARK1, MARK4, MAX, MBD1, MBTPS2, MC1R, MC2R, MCC, MCL1, MCM4, MDH2, MDM2, MDM4, MECOM, MEFV, MEN1, MET, MFN2, MGAT2, MGMT, MINPP1, MIR142, MITF, MLH1, MLH3, MLL, MLLT10, MMP1, MMP2, MN1, MNX1, MPL, MPL, MPLKIP, MRAP, MRE11, MRE11A, MS4A1, MSH2, MSH3, MSH6, MSL3, MSR1, MST1R, MSTO1, MSX2, MTAP, MTHFR, MTM1, MTMR14, MTOR, MTR, MTRR, MUC1, MUC5B, MUTYH, MVD, MVK, MXI1, MYB, MYC, MYCL1, MYCN, MYD88, MYH11, MYH8, MYH9, MYLK, MYO1H, MYSM1, NAGS, NBEAL2, NBN, NCOA1, NCOA2, NCOA4, NCOR1, ND5, NDP, NDUFAF6, NEK1, NEK9, NEUROD1, NF1, NF2, NFE2L2, NFE2L3, NFKB1, NFKB2, NHP2, NIN, NKX2-1, NLRP1, NNT, NOD2, NODAL, NOP10, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NPM1, NQO2, NR0B1, NR4A3, NR5A1, NR5A2, NRAMP1, NRAS, NSD1, NSD2, NSUN2, NTRK1, NTRK3, NUMA1, NUP214, NUP98, OCA2, OCRL, OFD1, OGG1, OPCML, P2RX7, PADI6, PAK3, PALB2, PALLD, PARG, PARN, PARP1, PAX3, PAX4, PAX5, PAX6, PAX7, PAX8, PBRM1, PBX1, PCBP1, PCGF2, PCNA, PDCD10, PDE4DIP, PDE6D, PDGFB, PDGFRA, PDGFRB, PDGFRL, PDX1, PER1, PERP, PGAP3, PGM3, PGR, PHB, PHF21A, PHF6, PHKA2, PHKG2, PHOX2B, PICALM, PIEZO2, PIGG, PIGL, PIGU, PIK3C2B, PIK3CA, PIK3CB, PIK3CD, PIK3CG, PIK3R1, PIK3R2, PIM1, PKD1, PKD2, PKHD1, PLA2G2A, PLCB4, PLCD1, PLCG1, PLEKHG5, PML, PMS1, PMS2, PMVK, PNP, POFUT1, POGLUT1, POLD1, POLE, POLH, POLQ, POLR1B, POLR1C, POLR1D, POR, PORCN, POT1, POU5F1, POU6F2, PPARG, PPM1D, PPOX, PPP1CB, PPP2R1A, PPP2R1B, PRCC, PRDM1, PRDM16, PRF1, PRKACB, PRKAR1A, PRKCD, PRKDC, PRKN, PRLR, PRSS1, PRX, PSAP, PSCA, PSENEN, PSIP1, PTCH1, PTCH2, PTEN, PTGS2, PTH1R, PTPN11, PTPN12, PTPRD, PTPRJ, PTPRT, PUF60, PURA, PYGL, RAB4A, RABL3, RAD21, RAD50, RAD51, RAD51C, RAD51D, RAD54B, RAD54L, RAF1, RAG1, RAG2, RALGDS, RARA, RASA1, RASA2, RASAL1, RASGRP1, RB1, RB1CC1, RBBP6, RBPJ , RECQL, RECQL4, REL, RELA, RERE, REST, RET, RFWD3, RHBDF2, RHOH, RINT1, RIT1, RMRP, RNASEH2A, RNASEH2B, RNASEH2C, RNASEL, RNF113A, RNF139, RNF2, RNF213, RNF43, RNF6, RNR1, ROS1, RPGRIP1L, RPL10, RPL11, RPL15, RPL18, RPL22, RPL26, RPL27, RPL35, RPL35A, RPL5, RPS10, RPS14, RPS15A, RPS17, RPS19, RPS20, RPS24, RPS26, RPS27, RPS28, RPS29, RPS6KA2, RPS7, RRAS, RRAS2, RRM1, RSPO1, RSPRY1, RTEL1, RUNX1, RUNX1T1, RYR1, SAMD9, SAMD9L, SAMHD1, SASH1, SBDS, SCG5, SCN10A, SCN11A, SCN4A, SCN9A, SDHA, SDHAF2, SDHB, SDHC, SDHD, SEC23A, SEC23B, SEMA4A, SEPT9, SERPINA1, SETBP1, SETD2, SF3B1, SFTPA2, SFTPC, SGK1, SH2B3, SH2D1A, SH3GL1, SH3KBP1, SHH, SHOC2, SHOX, SIN3A, SIX1, SIX3, SIX6, SKAP1, SKI, SKIV2L, SLC12A3, SLC17A9, SLC22A18, SLC25A11, SLC25A13, SLC26A2, SLC26A4, SLC2A2, SLC37A4, SLC45A2, SLC6A17, SLCO2A1, SLX4, SLX4, SMAD2, SMAD4, SMAD4, SMAD7, SMARCA4, SMARCAD1, SMARCAL1, SMARCB1, SMARCC2, SMARCD1, SMARCD2, SMARCE1, SMC1A, SMC3, SMO, SMPD1, SMUG1, SNAI2, SOCS1, SOS1, SOS2, SOX11, SOX17, SOX2, SOX4, SOX6, SOX9, SPEN, SPINK1, SPOP, SPRED1, SPRTN,

SPTBN1, SQSTM1, SRC, SRD5A2, SRD5A3, SREBF1, SRGAP1, SRP54, SRP72, SRP72, SRY, SSX1, SSX2, STAC3, STAG2, STAG3, STAR, STAT1, STAT3, STIL, STIM1, STK36, STK4, STS, STX11, STXBP2, SUFU, SYK, SYNE1, TACC3, TAF1, TAF15, TAF1L, TAL1, TAL2, TARS1, TBC1D24, TBL1XR1, TBX18, TBX2, TBX22, TBX3, TBXT, TCF12, TCF3, TCF4, TCF7L1, TCF7L2, TCIRG1, TCL1A, TCOF1, TCTN3, TEK, TENT5A, TERC, TERT, TET1, TET2, TFAP2A, TFE3, TG, TGFBR1, TGFBR2, TGIF1, TGM7, THBS1, THPO, TIMP3, TINF2, TIPARP, TJP2, TLR4, TLX1, TMC6, TMC8, TMEM107, TMEM127, TMEM216, TMEM231, TMEM67, TNFAIP3, TNFRSF10B, TNFRSF13B, TNFRSF13C, TNFRSF14, TNFRSF4, TNK2, TNPO3, TNRC6B, TOP1, TP53, TP63, TPP2, TPR, TRAF7, TREM2, TREX1, TRIM24, TRIM33, TRIM37, TRIP11, TRIP13, TRNF, TRNK, TRNL1, TRNP, TRNQ, TRNS1, TRNS2, TRPS1, TRPV3, TRRAP, TSC1, TSC2, TSHR, TSHZ2, TSHZ3, TSR2, TTC37, TTPP3, TUBB, TWIST1, TXNRD2, TYR, TYROBP, U2AF1, UBA1, UBE2T, UBR5, UGT1A1, UNC13D, UROD, UROS, USB1, USP8, USP9X, USP9X, VANGL1, VANGL2, VDR, VEGFC, VEZF1, VHL, VPS16, WAS, WASHC5, WDPCP, WHSC1, WIPF1, WNT10A, WNT5A, WRAP53, WRN, WT1, WWOX, XIAP, XPA, XPC, XPO1, XRCC2, XRCC3, XRCC4, YY1, ZAP70, ZFHX3, ZFPM2, ZIC2, ZNF384, ZNF521, ZSWIM6

Incidental genes: The design of the panel is based on the ACMG (American College of Medical Genetics and Genomics) SF v.3.0 recommendations (https://www.nature.com/articles/s41436-021-01172-3).

ACTA2, ACTC1, ACVRL1, APC, APOB, ATP7B, BMPR1A, BRCA1, BRCA2, BTD, CACNA1S, CASQ2, COL3A1, DSC2, DSG2, DSP, ENG, FBN1, FLNC, GAA, GLA, HFE, HNF1A, KCNH2, KCNQ1, LDLR, LMNA, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, MYBPC3, MYH11 MYH7, MYL2, MYL3, NF2, OTC, PALB2, PCSK9, PKP2, PMS2, PRKAG2, PTEN, RB1, RET, RPE65, RYR1, RYR2, SCN5A, SDHAF2, SDHB, SDHC, SDHD, SMAD3, SMAD4, STK11, TGFBR1, TGFBR2, TMEM127, TMEM43, TNNI3, TNNT2, TP53, TPM1, TRDN, TSC1, TSC2, TTN, VHL, WT1.

Variant interpretation: All candidate variants were evaluated with respect to their pathogenicity and causality, and these are categorized following ACMG guidelines (PMID: 25741868). All variants are verified to have good quality, and only those variants with evidence for causing or contributing to disease are reported as primary findings. The variants are classified following the 5-tier classes: pathogenic, likely pathogenic, variants of uncertain significance (VUS), likely benign and benign. Likely benign and benign variants are not reported. Incidental findings that do not correlate with the provided phenotype(s) are reported according to ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing (PMID: 23788249), if consented.

Limitations

The genetic result's interpretation is strongly dependent on the clinical information (preferably based on HPO) and family history. Misinterpretation may occur if this data not provided correctly or completely. The knowledge about the frequency of variants is growing and databases are updating, therefore the reclassification of variants is expected.

Variants in the intronic, UTR and promoter regions are not intended to be detected by this assay. This test does not detect complex inversions, gene conversions, balanced translocations, repeat expansion. Therefore, it is possible that the gene region where pathogenic variant is located, could not be sequenced using the current technology of this test and therefore was not detected.

It is possible that a particular genetic variant may not be recognized as the underlying cause of the genetic disorder due to incomplete scientific knowledge about the biological function of all genes in the human genome and the impact of variants in those genes.

Signatures

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